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(54) Title: SECRETED SOLUBLE α2δ-2, α2δ-3 OR α2δ-4 CALCIUM CHANNEL SUBUNIT POLYPEPTIDES AND SCREENING ASSAYS USING SAME

(57) Abstract: The present invention relates to secreted soluble α2δ-2, α2δ-3 or α2δ-4 calcium channel subunit polypeptides and their preparation, corresponding nucleic acids, recombinant vectors and host cells, as well as screening assays using same.

WO 01/19870 A2

Secreted soluble α2δ-2, α2δ-3 or α2δ-4 calcium channel subunit polypeptides and screening assays using same

FIELD OF THE INVENTION

The present invention relates to soluble α2δ-2, α2δ-3 or α2δ-4 calcium channel subunits and their preparation, corresponding nucleic acids, recombinant vectors and host cells comprising the same, as well as screening assays using same.The present invention relates to secreted soluble α2δ-2, α2δ-3 or α2δ-4 calcium channel subunit polypeptides and their preparation, corresponding nucleic acids, recombinant vectors and host cells, as well as screening assays using same

BACKGROUND OF THE INVENTION

Voltage-dependent Ca^{2+}channels (VDCCs) are heteromultimeric complexes present in both neuronal and non-neuronal tissues, including heart and skeletal muscle. VDCCs are minimally composed of three subunits: a pore-forming transmembrane α_1 subunit, a hydrophilic intracellular β subunit, and a membrane-associated $\alpha_2\delta$ subunit; a transmembrane γ subunit is also found in skeletal muscle tissue. Multiple subtypes and/or splice variants of the α_1, β, and $\alpha_2\delta$ subunits have been found.

Gabapentin ((1-aminomethyl)cyclohexane acetic acid or Neurontin) is a structural analogue of GABA, which is mainly used as an adjunctive therapy for epilepsy. Recent research suggests that gabapentin may also have clinical utility for various indications including anxiety and pain. Although designed as a lipophilic GABA-mimetic, gabapentin does not have a high affinity for either $GABA_A$ or $GABA_B$ receptors, GABA uptake sites, or the GABA-degrading enzyme GABA-transaminase (EC 2.6.1.19).

A novel high affinity binding site for [^{3}H]gabapentin in rat, mouse, and porcin brains has been characterized. Recently, the [^{3}H]gabapentin-binding protein was isolated from pig brain and identified as the $\alpha_2\delta$-1 subunit of VDCCs. None of the prototypic anticonvulsant drugs displace [^{3}H]gabapentin binding from the $\alpha_2\delta$-1 subunit. [^{3}H]Gabapentin-binding is stereospecifically inhibited by two enantiomers of 3-isobutyl GABA. The rank order of potency of gabapentin, and S- and R-isobutyl GABA, at the [^{3}H]gabapentin binding site mirrors their anticonvulsant activity in mice. However, electrophysiological studies have yielded conflicting data on the action of gabapentin at VDCCs.

The $\alpha_2\delta$ subunit is derived from a single gene, the product of which is extensively post-translationally modified particularly through the cleavage of the signal sequence. The polypeptide is cleaved to form disulfide-bridged α_2 and δ peptides, both of which are heavily glycosylated. Although it seems clear today that the α_2 and δ peptides are membrane-associated peptides, it is unclear whether these peptides comprise one or several transmembrane domains. Furthermore, the location, size and structural configuration of these eventual transmembrane domains remains to be determined.

But in any event, the fact that $\alpha_2\delta$ is a membrane-associated protein, regardless of its precise structural configuration, renders its large scale expression in recombinant systems difficult. Indeed, as the $\alpha_2\delta$ protein is targeted to the membrane, it requires detergent solubilisation to release it for purification. This important drawback imposes considerable restrictions for any potential applications requiring large amounts of recombinant protein. Furthermore, the various subtypes of $\alpha_2\delta$ subunits are different proteins with very low homologies. It is therefore extremely difficult to predict their respective behaviors, for example in gene truncation experiments.

The only assay currently available for the screening of ligands that bind the $\alpha_2\delta$ subunit involves the use of pig membrane extracts as a source of the $\alpha_2\delta$ subunit. Such an assay presents major inconvenients. Firstly, because the assay material is a membrane extract, it is very difficult to accurately determine the protein composition from one assay preparation to another particularly with regard to the subtype. Also, the presence of various impurities in the assay preparation is a problem in small plate assays. Furthermore, as the protein preparation lacks homogeneity, the interaction between the targeted protein and the assay plate is often quite uneven. This renders the streamlining of the assay in a high throughput format almost impossible to achieve.

SUMMARY OF THE INVENTION

The invention relates to forms of calcium channel $\alpha_2\delta$ subunits that are soluble and retain the functional characteristics of the full-length or wild-type $\alpha_2\delta$ subunit from which they derive.

In particular, the invention relates to forms of calcium channel $\alpha2\delta$-2, $\alpha2\delta$-3 or $\alpha2\delta$-4 subunits that are soluble and retain the functional characteristics of the full-length or wild-type $\alpha_2\delta$ subunit from which they derive.

In the context of the present invention, a calcium channel $\alpha_2\delta$ subunit, in particular a calcium channel $\alpha 2\delta$-2, $\alpha 2\delta$-3 or $\alpha 2\delta$-4 sub-unit, is preferably a mammalian calcium channel $\alpha_2\delta$ subunit, in particular human or porcine.

In the context of the present invention, a calcium channel is preferably of cerebral cortical origin and/or voltage-dependent.

In the context of the present invention, the inventors have found that it was possible to delete a portion of the nucleotide sequence encoding a eukaryotic, preferably a mammal cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$ subunit to yield a soluble secreted protein which retains its affinity for [^{3}H]gabapentin.

Preferably, a "soluble form" means a form that is not membrane-associated. In particular, a "soluble form" means a form lacking membrane anchorage, a purified form, an isolated form, a free form and/or a secreted form.

Preferably, the "functional characteristics of the full-length or wild-type $\alpha_2\delta$ subunit" are the affinity for, the binding of or the interaction with ligands, especially [^{3}H]gabapentin, gabapentin and/or spermine.

The invention concerns:

1) A purified or isolated nucleic acid encoding a mammalian secreted soluble cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide.

2) A purified or isolated nucleic acid according to 1), comprising a polynucleotide having at least 90% identity with the sequence encoding :

- from amino-acid 1 to between amino-acids 1027 and 1062 of SEQ ID N°20 for $\alpha_2\delta$-2,
- from amino-acid 1 to between amino-acids 984 and 1019 of SEQ ID N°22 for $\alpha_2\delta$-3.

3) A purified or isolated nucleic acid according to 1), having at least 90% identity with the sequence encoding :

- from amino-acid 1 to between amino-acids 1047 and 1062 of SEQ ID N°20 for $\alpha_2\delta$-2,
- from amino-acid 1 to between amino-acids 1004 and 1019 of SEQ ID N°22 for $\alpha_2\delta$-3.

4) A purified or isolated nucleotide sequence according to 1) wherein said sequence is the sequence of SEQ ID N°1, SEQ ID N°2, SEQ ID N°3, SEQ ID N°7, SEQ ID N°8,

SEQ ID N°9, SEQ ID N°13, SEQ ID N°14, SEQ ID N°15, SEQ ID N°19 or SEQ ID N°21.

5) A purified or isolated nucleic acid, having at least 90% identity with the nucleotide sequence of SEQ ID N°19 or SEQ ID N°21.

6) A purified or isolated polynucleotide comprising at least 10 consecutive nucleotides of the nucleotide sequence of SEQ ID N°19 or SEQ ID N°21.

7) A polynucleotide probe or primer hybridizing, under stringent conditions, with the nucleotide sequence of SEQ ID N°19 or SEQ ID N°21.

8) A method for the amplification of a nucleic acid encoding a mammalian secreted soluble cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$-n subunit polypeptide wherein n is 2, 3 or 4, said method comprising the steps of:

(a) contacting a test sample suspected of containing the target secreted soluble $\alpha_2\delta$-n subunit nucleic acid, or a sequence complementary thereto, with an amplification reaction reagent comprising a pair of amplification primers located on either side of the $\alpha_2\delta$-n subunit nucleic acid region to be amplified, and

(b) optionally, detecting the amplification products.

9) A kit for the amplification of a nucleic acid encoding a secreted soluble $\alpha_2\delta$-n subunit polypeptide wherein n is 2, 3 or 4, or a complementary sequence thereto in a test sample, wherein said kit comprises:

(a) a pair of oligonucleotide primers which can hybridize, under stringent conditions, to the secreted soluble $\alpha_2\delta$-n subunit nucleic acid region to be amplified;

(b) optionally, the reagents necessary for performing the amplification reaction.

10) A recombinant vector comprising a nucleic acid according to any one of 1) to 6).

11) A recombinant host cell comprising a nucleic acid according to any one of 1) to 6) or a vector according to 10).

12) A method for producing a secreted soluble $\alpha_2\delta$-n subunit wherein n is 2, 3 or 4, and said method comprises the steps of:

(a) inserting the nucleic acid encoding the desired $\alpha_2\delta$-n subunit polypeptide in an appropriate vector;

(b) culturing, in an appropriate culture medium, a host cell previously transformed or transfected with the recombinant vector of step (a);

(c) harvesting the culture medium thus obtained or lyse the host cell, for example by sonication or osmotic shock;

(d) separating or purifying, from said culture medium, or from the pellet of the resultant host cell lysate, the thus produced $\alpha_2\delta$-n subunit polypeptide of interest.

13) A purified or isolated recombinant polypeptide comprising the amino acid sequence of a secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide.

14) A recombinant polypeptide according to 13), having at least 80% amino-acid identity with a polypeptide comprising :

- from amino acid 1 to between amino acids 1027 and 1062 of the amino acid sequence of SEQ ID N°20, or
- from amino acid 1 to between amino acids 1019 and 1079 of the amino acid sequence of SEQ ID N°22.

15) A recombinant polypeptide according to 14), wherein said recombinant polypeptide is selected from the group consisting of the amino acid sequences of SEQ ID n°4, SEQ ID n°5, SEQ ID n°6, SEQ ID n°10, SEQ ID n°11, SEQ ID n°12, SEQ ID n°16, SEQ ID n°17, SEQ ID n°18, SEQ ID n°23 and SEQ ID n°24.

16) A method for the screening of ligands which bind a cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$-n subunit wherein n is 2, 3 or 4, said method comprising the steps of:

- contacting a secreted soluble recombinant calcium channel $\alpha_2\delta$-n subunit polypeptide with:
  - a ligand of interest; and
  - a labelled compound which binds the $\alpha_2\delta$-n subunit; and
- measuring the level of binding of the labelled compound to the $\alpha_2\delta$-n subunit.

17) A method according to 16), wherein said method is a scintillation proximity assay.

18) A method according to 16), wherein said method is a flashplate assay.

19) A method according to 16), wherein said method is a filter binding assay.

20) A method according to 16), wherein said secreted soluble recombinant calcium channel $\alpha_2\delta$-n subunit polypeptide is selected from polypeptides having at least 80%, preferably 90%, more preferably 95%, and most preferably 98 or 99% amino-acid identity with the polypeptide comprising from amino acid 1 to between amino-acids 984 and 1063, preferably between amino-acids 994 and 1054, and most preferably between amino-acids 1019 and 1054 of SEQ ID N°5 or SEQ ID N°16.

21) A method according to 16), wherein said secreted soluble recombinant calcium channel $\alpha_2\delta$-n subunit polypeptide is selected from the group consisting of SEQ ID N°4, 5, 6, 10, 11, 12, 16, 17 and 18,

22) A kit for the screening of ligands which bind a cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$-n subunit wherein n is 2, 3 or 4, said kit comprising:

- a secreted soluble recombinant calcium channel $\alpha_2\delta$-n subunit; and
- a labelled compound which binds to the $\alpha_2\delta$-n subunit.

Hence, the invention concerns nucleotide sequence fragments of a cerebral cortical voltage dependent calcium channel $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit cDNA encoding a soluble secreted $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide (hereinafter a $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit). Preferably, these nucleotide sequences encode a soluble secreted $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide bearing a gabapentin or a [^{3}H]gabapentin binding site. More preferably, the soluble secreted $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit nucleic acid is derived from a eukaryotic, preferably a mammal, more preferably a human $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit.

bearing a gabapentin or a [^{3}H]gabapentin binding site

A further object of the present invention concerns recombinant vectors comprising a nucleic acid sequence encoding a soluble secreted $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide.

The invention also encompasses host cells and transgenic non-human mammals comprising said nucleic acid sequences or recombinant vectors.

The invention also concerns a soluble secreted $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide which is characterized in that it is a soluble secreted polypeptide having affinity for

[^{3}H]gabapentin. Preferably, the soluble secreted polypeptide is derived from a mammal, more preferably a human $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit.

The inventors have also found that it was possible to use a soluble secreted form of a voltage-dependant calcium channel $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide in an assay for the screening of ligands which bind the $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit.

The invention therefore also concerns a method for the screening of ligands which bind a calcium channel $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit.
The method comprises the steps of:

- contacting a secreted soluble recombinant calcium channel $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide with:
  - a ligand of interest; and
  - a labelled compound which binds a $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit; and
- measuring the level of binding of the labelled compound to the secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit.

The invention also concerns a kit for the screening of ligands which bind a calcium channel $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit.
The kit comprises:

- a secreted soluble recombinant calcium channel $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide; and
- a labelled compound which binds a calcium channel $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit.

The invention also concerns :

1) A calcium channel $\alpha_2\delta$ subunit that is soluble and retain the functional characteristics of the full-length or wild-type $\alpha_2\delta$ subunit from which it derives.

2) A calcium channel $\alpha_2\delta$ subunit according to 1) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is of mammalian origin.

3) A calcium channel $\alpha_2\delta$ subunit according to 2) above wherein the mammalian origin is a human, a porcine, a rat or a mouse origin.

4) A calcium channel $\alpha_2\delta$ subunit according to 3) above wherein the mammalian origin is a human origin.

5) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 4) above, wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is naturally expressed in the cerebral cortical.

6) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 5) above, wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is voltage-dependent.

7) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 6) above, wherein the $\alpha_2\delta$ subunit is cleaved.

8) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 7) above, wherein the $\alpha_2\delta$ subunit is cleaved into separate α_2 and δ peptides.

9) A calcium channel $\alpha_2\delta$ subunit according to 8) above, wherein the α_2 and δ peptides are disulfide-bridged.

10) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 6) above, wherein the $\alpha_2\delta$ subunit is not cleaved.

11) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 10) above characterized in that it is purified or isolated.

12) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 11) above characterized in that it is processed as the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is naturally processed.

13) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 12) above characterized in that it is producable by the baculovirus/insect cells expression system.

14) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 13) above characterized in that it is produced by the baculovirus/insect cells expression system.

15) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 14) above characterized in that its δ peptide comprises at least the ligand-interacting part(s) of the complete δ peptide from which it originates

16) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 15) above characterized in that its δ peptide has a C-terminal truncation with respect to the complete δ peptide from which it originates, said truncation being sufficient to render the truncated δ peptide soluble.

17) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 16) above characterized in that its α_2 peptide comprises at least the ligand-interacting part(s) of the complete α_2 peptide from which it originates.

18) A calcium channel $\alpha_2\delta$ subunit according to any one of 15) or 17) above characterized in that ligand is gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine, Spermine or L-Phenylalanine.

19) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 18) above characterized in that its α_2 peptide comprises at least the ligand-interacting part(s) of the

complete α_2 peptide from which it originates, its δ peptide comprises at least the ligand-interacting part(s) of the complete δ peptide from which it originates and its δ peptide does not comprise a part of the transmembrane domain of the complete δ peptide from which it originates which renders said calcium channel insoluble.

20) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 19) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates is *$\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4.*

21) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 20) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°20.

22) A calcium channel $\alpha_2\delta$ subunit according to 20) or 21) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 4, SEQ ID N° 5 or SEQ ID N° 6.

23) A calcium channel $\alpha_2\delta$ subunit according to any one of 20) to 22) above characterized in that the amino acid sequence of its unprocessed form comprises the region comprised between amino acid number 340 and amino acid number 1062 of SEQ ID N°20.

24) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 20) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°21.

25) A calcium channel $\alpha_2\delta$ subunit according to 20) or 24) characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 10, SEQ ID N° 11 or SEQ ID N° 12.

26) A calcium channel $\alpha_2\delta$ subunit according to any one of 20), 24) or 25) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 306 and amino acid number 1019 of SEQ ID N°20.

27) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 20) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°55.

28) A calcium channel $\alpha_2\delta$ subunit according to 20) or 27) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 53, SEQ ID N° 54 or SEQ ID N° 55.

29) A calcium channel $\alpha_2\delta$ subunit according to any one of 20), 27) or 28) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 302 and amino acid number 1050 of SEQ ID N°55.

30) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 20) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°33 or SEQ ID N°44.

31) A calcium channel $\alpha_2\delta$ subunit according to 20) or 30) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 34, SEQ ID N° 35, SEQ ID N° 36, SEQ ID N° 41, SEQ ID N° 42 or SEQ ID N° 43.

32) A calcium channel $\alpha_2\delta$ subunit according to any one of 20), 30) or 31) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 302 and amino acid number 1018 of SEQ ID N°33 or SEQ ID N°44.

33) A calcium channel $\alpha_2\delta$ subunit according to any one of 20), 30) or 31) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 302 and amino acid number 1018 of SEQ ID N°33 or SEQ ID N°44.

34) A calcium channel $\alpha_2\delta$ subunit according to any one of 20), 30), 31), 32) or 33) above characterized in that its α_2 peptide comprises the region comprised between amino acid number 302 and amino acid number 946 or 997 of SEQ ID N°33 or of SEQ ID N°44 and its δ peptide comprises the region comprised between amino acid number 984 and amino acid number 1018 of SEQ ID N°33 or of SEQ ID N°44.

35) A calcium channel $\alpha_2\delta$ subunit characterized in that its α_2 peptide and its δ peptide have 99%, 98%, 97%, 96%, or 95% homology or identity with the α_2 peptide and the δ peptide respectively of a calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 34) above.

36) A nucleic acid molecule characterized in that its nucleotide sequence comprises a nucleotide sequence which encodes a calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 35) above.

37) A nucleic acid molecule characterized in that its nucleotide sequence comprises a nucleotide sequence which encodes the α_2 peptide or the δ peptide of a calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 35) above.

38) A nucleic acid molecule which hybridizes under stringent conditions with a nucleic acid molecule according to 36) or 37) above or 39) herebelow.

39) A nucleic acid molecule according to any one of 36) to 38) above which comprises SEQ ID N°1, SEQ ID N°2, SEQ ID N°3, SEQ ID N°7, SEQ ID N°8, SEQ ID N°9, SEQ ID N°13, SEQ ID N°14, SEQ ID N°15, SEQ ID N°30, SEQ ID N°31, SEQ ID N°32, SEQ ID N°38, SEQ ID N°39, SEQ ID N°40, SEQ ID N°50, SEQ ID N°51, or SEQ ID N°52.

40) A vector capable of expressing a nucleic acid molecule according to any one of 36) to 39) above.

41) An expression vector comprising a nucleic acid molecule according to any one of 36) to 39) above.

42) A vector according to 40) or 41) above which is a baculovirus vector.

43) A cell comprising a nucleic acid molecule according to any one of 36) to 39) above.

44) A cell comprising a vector according to 40), 41) or 42) above.

45) A cell according to 43) or 44) above which is a mammalian cell or an insect cell.

46) A composition comprising a calcium channel $\alpha_2\delta$ subunit according to any one of 7) to 9) above and a calcium channel $\alpha_2\delta$ subunit according to 10) above.

47) Screening assay using a calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 35) above.

48) Screening assay according to 47) above which is an SPA assay, a Flashplate assay, a Nickel Flasplate assay, a Filter binding assay or a Wheat Germ Lectin flasplate assay.

49) Use of screening assay according to 47) or 48) above to detect or measure the binding or interaction of a ligand of a calcium channel $\alpha_2\delta$ subunit and a calcium channel $\alpha_2\delta$ subunit.

50) Use according to 49) above wherein the ligand is gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine, Spermine or L-Phenylalanine.

51) Kit to detect or measure the binding or interaction of a ligand of a calcium channel $\alpha_2\delta$ subunit and a calcium channel $\alpha_2\delta$ subunit comprising a calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 35) above.

52) Kit according to 51) above wherein the ligand is gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine, Spermine or L-Phenylalanine.

53) Kit according to 51) or 52) above usable in an SPA assay, a Flashplate assay, a Nickel Flasplate assay, a Filter binding assay or a Wheat Germ Lectin flasplate assay.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates the dose response nature of [^{3}H]gabapentin binding s-$\alpha_2\delta$-2-6His and the maintenance of a constant low-level of non-specific binding (around 30-60cpm) independent of protein volume assayed.

Figure 2 illustrates the dose response nature of [^{3}H]gabapentin binding s-$\alpha_2\delta$-2-6His in the Nickel flashplate assay. As in the filter-binding assay, the level of non-specific binding is low (around 70-100cpm) and stable, independent of the volume of protein assayed or the point analysed on the time-course. A stable window is maintained for a period of at least 50 hours (between ~20 and 70 hours on the time-course)

Figure 3 illustrates the dose response nature of [^{3}H]gabapentin binding s-$\alpha_2\delta$-2-6His in the Wheat Germ lectin flashplate assay. Once again the level of non-specific binding is low (around 50-70cpm) and stable, independent of the volume of protein assayed or the point analysed on the time-course. The window is relatively stable over an extended period of time with just a gradual decline from the 15-hour time point (approximately 10% of the window every 24 hours).

DETAILED DESCRIPTION OF THE INVENTION

The invention concerns truncated $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit cDNA sequences. These truncated sequences encode soluble secreted polypeptides which retain their affinity for [^{3}H]gabapentin.

Throughout the present specification, the expression "nucleotide sequence" is used to designate indifferently a polynucleotide or a nucleic acid. More precisely, the expression "nucleotide sequence" encompasses the nucleic material and the sequence information and is not restricted to the sequence information (i.e. the succession of letters chosen among the four base letters) that biochemically characterizes a specific DNA or RNA molecule.

As used interchangeably herein, the terms "oligonucleotides", "nucleic acids" and "polynucleotides" include RNA, DNA, or RNA/DNA hybrid sequences of more than one nucleotide in either single chain or duplex form.

Further to its general meaning understood by the one skilled in the art, the term "nucleotide" is also used herein to encompass modified nucleotides which comprise at least one of the following modifications (a) an alternative linking group,.(b) an analogous form of purine, (c) an analogous form of pyrimidine, or (d) an analogous sugar. For examples of analogous linking groups, purines, pyrimidines, and sugars, see for example PCT publication N°WO 95/04064.

The polynucleotide sequences of the invention may be prepared by any know method, including synthetic, recombinant, or a combination thereof as well as through any purification methods known in the art.

A) Secreted α2δ-2, α2δ-3 or α2δ-4 subunit polypeptides

The invention comprises polynucleotide sequences encoding a soluble secreted eukaryotic, preferably a soluble secreted mammal $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide. These sequences particularly include but are not restricted to 1) those sequences encoding a soluble secreted polypeptide of this $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit which preferably retains its binding affinity for [^{3}H]gabapentin and 2) nucleotide fragments useful as nucleic acid primers or probes for amplification or detection purposes.

The expression "soluble secreted $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit" is intended to designate polypeptide sequences which, when produced by a recombinant host cell, are secreted at least partially into the culture medium rather than remaining associated with the host cell membrane.

1) cDNA fragments encoding soluble secreted $\alpha_2\delta$-2, $\alpha_2\delta$-3, $\alpha_2\delta$-4 subunit polypeptides

One of the important embodiments of the present invention concerns truncated nucleotide sequences of $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit cDNAs which encode soluble secreted $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptides. The inventors have found that it was possible to generate deletion mutants of $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit cDNAs which, when expressed, produce a significant amount of soluble secreted proteins, preferably soluble secreted proteins, which retain their [^{3}H]gabapentin binding affinity. These truncated nucleotide sequences of the invention are of significant value to the skilled person as they now allow fast and reliable access to significant concentrations of selected soluble secreted $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptides. To that end, the inventors have determined the minimal and optimal fragment lengths required to express a polypeptide which: 1) binds [^{3}H]gabapentin with sufficient affinity and; 2) is obtained in a soluble secreted form.

The discussion provided below provides comments on possible truncations, giving as an example the human $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit. However, given the very substantial cross-species homology for $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit sequences, the comments below can also be applied to other eukaryotic species, and more particularly other mammalian species such as rat, mouse, rabbit or pig. Their $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit sequences, which for most are available in public databases, share a very substantial homology with the human $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit sequences.

The inventors believe that the soluble secreted $\alpha_2\delta$-2 subunit polypeptides which are as close as possible to the native sequence and which are therefore more likely to retain

their native folding and hence their [^{3}H]gabapentin binding properties are those corresponding to the native protein in which amino-acid stretch 1027 to the C-terminal end of the amino-acid sequence of SEQ ID N°20 has been deleted. The skilled scientist can quite easily determine within this amino-acid stretch the optimal $\alpha_2\delta$-2 subunit polypeptides.

The inventors also believe that the soluble secreted $\alpha_2\delta$-3 subunit polypeptides which are as close as possible to the native sequence and which are therefore more likely to retain their native folding and hence thir [^{3}H]gabapentin binding properties are those corresponding to the native protein in which amino-acid stretch 984 to C-terminal end of the amino-acid sequence of SEQ ID N°22 has been deleted. The skilled scientist can quite easily determine within this amino-acid stretch the optimal $\alpha_2\delta$-3 subunit polypeptides.

The invention therefore particularly concerns a nucleotide sequence encoding a polypeptide having at least 80% identity with the polypeptide comprising from amino-acid 1 to between amino-acids 1027 and 1145, preferably to between amino-acids 1062 and 1145 of SEQ ID N°20.
Preferred nucleotide sequences include those of SEQ ID N°1, SEQ ID N° 2 and SEQ ID N°3.

The invention also concerns a nucleotide sequence encoding a polypeptide having at least 80% identity with the polypeptide comprising from amino-acid 1 to between amino-acids 984 and 1085, preferably tobetween amino-acids 1019 and 1085 of SEQ ID N°22.
Preferred nucleotide sequences include those of SEQ ID N°7, SEQ ID N° 8 and SEQ ID N°9.

The invention also encompasses isolated and/or purified nucleic acid molecules that hybridize under stringent conditions with the above nucleic acid sequences or a part thereof, and encode a soluble secreted $\alpha_2\delta$ subunit polypeptide having the ability to bind [^{3}H]gabapentin.

B) Amplification of the soluble secreted $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit nucleotide sequences

Another object of the invention consists of a method for the amplification of a nucleic acid encoding a soluble secreted $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide, preferably a polypeptide bearing a [^{3}H]gabapentin binding site, said method comprising the steps of:

(a) contacting a test sample suspected of containing the target $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit nucleic acid, a fragment or a variant thereof, or a sequence complementary thereto, with an amplification reaction reagent comprising a pair of amplification primers which can hybridize under stringent conditions, the $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit nucleic acid region to be amplified, and

(b) optionally, detecting the amplification products.

The expression [^{3}H]gabapentin binding site, when used herein is intented to designate a site which can bind either [^{3}H]gabapentin or other ligands such as (S+)-3-isobutyl gaba or (R-)-3-isobutyl gaba.

In a first preferred embodiment of the above method, the nucleic acid encodes a secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide of SEQ ID N°4, SEQ ID N°5, SEQ ID N°6, SEQ ID N°10, SEQ ID N°11, SEQ ID N°12, SEQ ID N°16, SEQ ID N°17 and SEQ ID n°18.

In a second preferred embodiment of the above amplification method, the amplification product is detected by hybridization with a labelled probe having a sequence which is complementary to the amplified region.

C) Recombinant vectors and hosts cells for the expression of a secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide

A most preferred system of expression of the calcium channel $\alpha_2\delta$ of the invention is the baculovirus/insect cell system. In fact, this system of expression allows to produce only the soluble form, is easy to use because the insect cells can be cultured without adherency and results in very high yield of production. Thus, this system allows mass-production of the calcium channel $\alpha_2\delta$ of the invention, provides an homogeneous production and is therefore particularly suitable for the preparation of this target for screening, in particular for high-throughput screening.

1) Recombinant vectors

The present invention also encompasses a family of recombinant vectors comprising any one of the nucleic acids described herein. Firstly, the invention deals with a recombinant vector comprising a nucleic acid selected from the group consisting of:

(a) a purified or isolated nucleic acid encoding a secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit having at least 80% amino acid identity with the polypeptide of SEQ ID N°20 or 22, or a sequence complementary thereto;

(b) a purified or isolated nucleic acid having at least 90% nucleotide identity with a polynucleotide selected from the group consisting of the nucleotide sequences of SEQ ID N°1, SEQ ID N°2, SEQ ID N°3, SEQ ID No 7, SEQ ID N°8, SEQ ID N°9, SEQ ID N°13, SEQ ID N°14, SEQ ID N°15 or a sequence complementary thereto;

(c) a purified or isolated polynucleotide comprising at least 10 consecutive nucleotides of a nucleic acid described in (a) or (b) or a sequence complementary thereto.

In a first preferred embodiment a recombinant vector of the invention is used to amplify the inserted polynucleotide of the invention in a suitable host cell, this polynucleotide being amplified every time the recombinant vector replicates.

Recombinant expression vectors comprising a nucleic acid encoding secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptides that are described in the present specification are also part of the invention. These include, but are not restricted to, nucleic acids encoding from amino-acid 1 to between amino-acids 1027 and 1145, preferably between amino-acids 1062 and 1145 of SEQ ID N°20, as well as nucleic acids encoding from amino-acid 1 to between amino-acids 984 and 1085, preferably between amino-acids 1019 and 1085, of SEQ ID N°22.

Another preferred embodiment of the recombinant vectors according to the invention consist of expression vectors comprising a nucleic acid encoding $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptides of the invention, and more preferably a nucleic acid encoding a polypeptide selected from the group consisting of the amino acid sequences of SEQ ID N°4, SEQ ID N°5, SEQ ID N°6, SEQ ID N°10, SEQ ID N°11, SEQ ID N°12, SEQ ID N°16, SEQ ID N°17 and SEQ ID n°18.

Within certain embodiments, expression vectors can be employed to express the secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptides which can then be purified and for example, be used as a immunogen in order to raise specific antibodies directed against said secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptides.

Preferred eukaryotic vectors of the invention are listed hereafter as illustrative but not limitative examples: pcDNA3, pFLAG, pCMV-Script, pIND, pMC1NEO, pHIL, pGAPZA, pMT/V5-His-TOPO, pMT/V5-His, pAc5.1/V5-HisA, pDS47/V5-His, pcDNA4, pcDNA6, pEF1, pEF4, pEF6, pUB6, pZeoSV2, pRc/CMv2, pcDM8, pCR3.1, pDisplay, pSecTag2, pVP22, pEMZ, pCMV/Zeo, pSinRep5, pCEP, pREP, pHook-1

Preferred bacteriophage recombinant vectors of the invention are P1 bacteriophage vectors such as described by Sternberg N.L. (1992;1994).

A suitable vector for the expression of a soluble secreted $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide is a baculovirus vector that can be propagated in insect cells and in insect cell-lines. Specific suitable host vectors includes, but are not restricted to :pFastBac-1, pIZ/V5-His, pBacMan-1, pBlueBac4.5, pBlueBacHis2, pMelBacA, pVL1392, pVL1393

The recombinant expression vectors from the invention may also be derived from an adenovirus such as those described by Feldman and Steig. (1996) or Ohno et al. (1994). Another preferred recombinant adenovirus according to this specific embodiment of the present invention is the human adenovirus type two or five (Ad 2 or Ad 5) or an adenovirus of animal origin (French Patent Application n°FR 93 05 954).

a) Regulatory expression sequences

Expression requires that appropriate signals are provided in the vectors, said signals including various regulatory elements such as enhancers/promoters from both viral and mammalian sources that drive expression of the genes of interest in host cells. The regulatory sequences of the expression vectors of the invention are operably linked to the nucleic acid encoding a soluble secreted $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide.

As used herein, the term "operably linked" refers to a linkage of polynucleotide elements in a functional relationship. For instance, a promoter or an enhancer is operably linked to a coding sequence if it affects the transcription of the coding sequence.

More precisely, two DNA molecules (such as a polynucleotide containing a promoter region and a polynucleotide encoding a desired polypeptide or polynucleotide) are said to be "operably linked" if the nature of the linkage between the two polynucleotides does not : (1) result in the introduction of a frame-shift mutation or (2) interfere with the ability of the polynucleotide containing the promoter to direct the transcription of the coding polynucleotide.

Generally, recombinant expression vectors include origins of replication, selectable markers permitting transformation of the host cell, and a promoter derived from a highly expressed gene to direct transcription of a downstream structural sequence. The heterologous structural sequence is assembled in an appropriate frame with the translation, initiation and termination sequences, and preferably a leader sequence capable of directing sequences of the translated protein into the periplasmic space or the extra-cellular medium.

In a specific embodiment wherein the vector is adapted for transfecting and expressing desired sequences in eukaryotic host cells, preferred vectors comprise an origin of replication from the desired host, a suitable promoter and an enhancer, and also any

necessary ribosome binding sites, polyadenylation site, transcriptional termination sequences, and optionally 5'-flanking non-transcribed sequences.

DNA sequences derived from the SV 40 viral genome, for example SV 40 origin early promoter, enhancer, and polyadenylation sites may be used to provide the required non-transcribed genetic elements.

b) Promoter sequences

Suitable promoter regions used in the expression vectors according to the invention are chosen taking into account the host cell in which the heterologous nucleic acids have to be expressed.

A suitable promoter may be heterologous with respect to the nucleic acid for which it controls the expression, or alternatively can be endogenous to the native polynucleotide containing the coding sequence to be expressed.

Additionally, the promoter is generally heterologous with respect to the recombinant vector sequences within which the construct promoter/coding sequence has been inserted.

Preferred eukaryotic promoters are the CMV, polyhidran or OPIE2.

2) Recombinant host cells

Host cells that have been transformed or transfected with one of the nucleic acids described herein, or with one of the recombinant vector, particularly recombinant expression vector, described herein are also part of the present invention.

Are included host cells that are transformed (prokaryotic cells) or are transfected (eukaryotic cells) with a recombinant vector such as one of those described above.

Preferred host cells used as recipients for the expression vectors of the invention are the following:

(a) prokaryotic host cells: *Escherichia coli*, strains. (i.e. DH10 Bac strain) *Bacillus subtilis, Salmonella typhimurium* and strains from species such as *Pseudomonas, Streptomyces* and *Staphylococcus;*

(b) eukaryotic host cells: HeLa cells (ATCC N°CCL2; N°CCL2.1; N°CCL2.2), Cv 1 cells (ATCC N°CCL70), COS cells (ATCC N°CRL 1650; N°CRL 1651), Sf-9 cells (ATCC N°CRL 1711), C127 cells (ATCC N°CRL-1804), 3T3 cells (ATCC N°CRL-6361), CHO cells (ATCC N°CCL-61), human kidney 293 cells (ATCC N° 45504; N°CRL-1573), BHK (ECACC N°84100 501; N°84111301), sf 9, sf 21 and hi-5 cells.

D) Production of recombinant secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptides

The present invention also concerns a method for producing one of the amino acid sequences described herein and especially a polypeptide selected from the group consisting of the aminoacid sequences of SEQ ID N°4, SEQ ID N°5, SEQ ID N°6, SEQ ID N°10, SEQ ID n°11, SEQ ID n°12, SEQ ID n°16, SEQ ID n°17 or SEQ ID n°18 wherein said method comprises the steps of:

(a) inserting the nucleic acid encoding the desired amino acid sequence in an appropriate vector;

(b) culturing, in an appropriate culture medium, a host cell previously transformed or transfected with the recombinant vector of step (a);

(c) harvesting the culture medium thus obtained or lyse the host cell, for example by sonication or osmotic shock;

(d) separating or purifying, from said culture medium, or from the pellet of the resultant host cell lysate, the thus produced recombinant polypeptide of interest.

In some instances, it is required to tag the secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide prior to purification. The tag is then in most instances encoded into the nucleotide sequence that is needed to express the polypeptide. Examples of such tags include, but are not limited to sequences encoding C-myc, FLAG, a sequence of histidine residues, heamaglutin A, V5, Xpress or GST. Most of these tags can be incorporated directly into the sequence, for instance through PCR amplification by incorporating the appropriate coding sequence in one of the PCR amplification primers. However, the tag can also be introduced by other means such as covalent binding of the appropriate nucleic acid sequence encoding the tag moiety with the 3' or 5' end of the nucleic acid sequence encoding the polypeptide sequence. This is the case for GST.

Purification of the recombinant secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3, $\alpha_2\delta$-4 subunit polypeptides according to the present invention is then carried out by passage onto a nickel or copper affinity chromatography column, such as a Ni NTA column or a Q-Sepharose column.

In another embodiment of the above method, the polypeptide thus produced is further characterized, for example by binding onto an immuno-affinity chromatography column on which polyclonal or monoclonal antibodies directed to the secreted soluble $\alpha_2\delta$-2 subunit polypeptide of interest have been previously immobilised.

In another embodiment of the invention, the secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3, $\alpha_2\delta$-4 subunit polypeptide can be only partially purified. For instance, it can be purified along with other contaminating proteins using an appropriate chromatography matrix such as an ion-exchange chromatography column. In such instances, it is not required to tag the desired polypeptide of interest.

The most preferred embodiment contemplated by the inventors concerns the use of a purified tagged secreted soluble $\alpha_2\delta$-2 , $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide. A particularly preferred tag is a nucleotide sequence encoding from 2 to 10, and preferably 6 histidine residues. Examples of such tagged polypeptides are depicted on SEQ ID N°23 and 24.

With regard to the secreted soluble $\alpha_2\delta$-2 , $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide used subsequently in the screening assay of the invention, several possibilities are also open to the skilled person.

In a first and preferred embodiment, the secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide comprises a tag moiety which can be selected among the tags referred to above. Such tagged polypeptides are particularly useful in SPA or flashplate assays. A preferred tag is the nucleotide sequence encoding histidine residues referred to above.

In a second embodiment, the secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide can be used without a tag. This is the case for instance in SPA or flashplate assays comprising beads or plates coated with wheat germ lectin. In such an embodiment, the tag is not needed as the carbohydrate moieties of the secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide bind directly to the wheat germ lectin-coated beads or plates.

E) Purified recombinant secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 polypeptides

Another object of the present invention consists of a purified or isolated recombinant polypeptide comprising the amino acid sequence of a secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide.

Preferred isolated recombinant polypeptides of the invention include those having at least 80%, preferably 90%, more preferably 95, and most preferably 98 or 99%, amino-acid identity with polypeptides comprising from amino acid 1 to between amino-acids 1027 and 1145, preferably between amino-acids 1062 and 1145 of SEQ ID N°20, as well as

those having at least 80%, preferably 90%, more preferably 95, and most preferably 98 or 99%, amino-acid identity with polypeptides comprising from amino acid 1 to between amino-acids 984 and 1085, preferably between amino-acids 1019 and 1085 of SEQ ID N°22.

In a further preferred embodiment, the polypeptide comprises an amino acid sequence having at least 80%, preferably 90%, more preferably 95%, and most preferably 98% or 99% amino acid identity with the amino acid sequence of SEQ ID N°4, SEQ ID N°5, SEQ ID N°6, SEQ ID N°10, SEQ ID N°11, SEQ ID N°12, SEQ ID N°16, SEQ ID N°17 and SEQ ID N°18

More generally, the invention encompasses any secreted soluble $\alpha_2\delta$ subunit polypeptide encoded by a nucleic acid of the present invention.

F) Modified secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptides

The invention also relates to secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide comprising amino acid changes ranging from 1, 2, 3, 4, 5, 10, 20, 25, 30, 35, 40 substitutions, additions or deletions of one amino acid as regards to polypeptides of anyone of the amino acid sequences of the present invention. Preferred sequences are those of SEQ ID N°4, SEQ ID N°5, SEQ ID N°6, SEQ ID N°10, SEQ ID N°11, SEQ ID n°12, SEQ ID n°16, SEQ ID n°17 and SEQ ID N°18.

In the case of an amino acid substitution in the amino acid sequence of a polypeptide according to the invention, one or several consecutive or non-consecutive amino-acids are replaced by "equivalent" amino-acids. The expression "equivalent" amino acid is used herein to designate any amino acid that may be substituted for one of the amino-acids belonging to the native protein structure without decreasing the binding properties of the corresponding peptides to the antibodies raised against the polypeptides of the invention. In other words, the "equivalent" amino-acids are those which allow the generation or the synthesis of a polypeptide with a modified sequence when compared to the amino acid sequence of the secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptides of interest, said modified polypeptide being able to bind to the antibodies raised against the secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide of interest and/or to induce antibodies recognizing the parent polypeptide.

Alternatively, amino acid changes encompassed are those which will not abolish the biological activity of the resulting modified polypeptide. These equivalent amino-acids may be determined either by their structural homology with the initial amino-acids to be replaced, by the similarity of their net charge or of their hydrophobicity, and optionally

by the results of the cross-immunogenicity between the parent peptides and their modified counterparts.

The peptides containing one or several "equivalent" amino-acids must retain their specificity and affinity properties to the biological targets of the parent protein, as it can be assessed by a ligand binding assay or an ELISA assay.

Examples of amino-acids belonging to specific classes include Acidic (Asp, Glu), Basic (Lys, Arg, His), Non-polar (Ala, Val, Leu, Ile, Pro, Met, Phe, Trp) or uncharged Polar (Gly, Seu, Thr, lys, Tyr, Asn, Gln) amino-acids.

Preferably, a substitution of an amino acid in $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide of the invention, or in a peptide fragment thereof, consists in the replacement of an amino acid of a particular class for another amino acid belonging to the same class.

By an equivalent amino acid according to the present invention is also contemplated the replacement of a residue in the L-form by a residue in the D form or the replacement of a Glutamic acid (E) residue by a Pyro-glutamic acid compound. The synthesis of peptides containing at least one residue in the D-form is, for example, described by Koch (1977).

A specific embodiment of a modified peptide of interest according to the present invention, includes, but is not limited to, a peptide molecule, which is resistant to proteolysis. This is a peptide in which the -CONH- peptide bond is modified and replaced by a (CH_2NH) reduced bond, a (NHCO) retro inverso bond, a (CH_2-O) methylene-oxy bond, a (CH_2S) thiomethylene bond, a (CH_2CH_2) carba bond, a (CO-CH_2) cetomethylene bond, a (CHOH-CH_2) hydroxyethylene bond), a (N-N) bound, a E-alcene bond or also a -CH=CH-bond.

The invention also encompasses secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide in which at least one peptide bond has been modified as described above.

The polypeptides according to the invention may also be prepared by the conventional methods of chemical synthesis, either in a homogenous solution or in solid phase. As an illustrative embodiment of such chemical polypeptide synthesis techniques, it may be cited the homogenous solution technique described by Houbenweyl (1974).

The secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide of interest, or a fragment thereof may thus be prepared by chemical synthesis in liquid or solid phase by successive couplings of the different amino acid residues to be incorporated (from the N-terminal end to the C-terminal end in liquid phase, or from the C-terminal end to the N-terminal end in solid phase) wherein the N-terminal ends and the reactive side chains are previously blocked by conventional groups.

For solid phase synthesis, the technique described by Merrifield (1965a; 1965b) may be used in particular.

G) Antibody production

The secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptides of the invention and their peptide fragments of interest can be used for the preparation of antibodies.

Polyclonal antibodies may be prepared by immunization of a mammal, especially a mouse or a rabbit, with a polypeptide according to the invention that is combined with an adjuvant of immunity, and then by purifying the specific antibodies contained in the serum of the immunized animal on an affinity chromatography column on which has previously been immobilized the polypeptide that has been used as the antigen.

Monoclonal antibodies may be prepared from hybridomas according to the technique described by Kohler and Milstein (1975).

The present invention also deals with antibodies produced by the trioma technique and by the human B-cell hybridoma technique, such as described by Kozbor et al. (1983).

Antibodies of the invention also include chimeric single chain Fv antibody fragments (US Patent N° 4,946,778; Martineau et al., (1998), antibody fragments obtained through phage display libraries Ridder et al. (1995) and humanized antibodies (Leger et al., (1997)).

H) Screening assays

The invention concerns a method for the screening of ligands which bind soluble secreted $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide. More particularly, the targeted $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit binding site is preferably the [^{3}H]gabapentin binding site. The various parameters of the method of the invention are described in further detail below.

1) Labelled compounds which bind the secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide

In cases where the $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 binding site is the [^{3}H]gabapentin binding site, the preferred labelled compound which can be used is of course gabapentin itself. However, gabapentin is not the only labelled compound which can be used in this context. Indeed, it has been previously demonstrated that saturation binding analyses on porcine synaptic plasma cerebral cortex membranes performed in the presence of L-leucine indicate a competitive interaction of the amino acid with the [^{3}H]gabapentin binding site, significantly reducing [^{3}H]gabapentin binding affinity for the site. The inventors believe that this competitive interaction is true across all the amino-acids listed in table 1 below.

TABLE 1

Binding affinities of selected amino acids (IC_{50} <500nM) for the [^{3}H]gabapentin site in porcine cortical membranes

COMPOUND	IC_{50} (nM) ARITHMETIC MEAN (N=3) ± S.E.M.
Gabapentin	42.1 ± 5.5
L-Norleucine	23.6 ± 6.7
L-Allo-Isoleucine	32.8 ± 6.0
L-Methionine	49.6 ± 10.0
L-Leucine	61.3 ± 20.9
L-Isoleucine	68.8 ± 1.9
L-Valine	330 ± 18
L-Phenylalanine	351 ± 89

It is therefore possible to use commercialy available labelled forms of these high affinity ligands in replacement of gabapentin. The utility of [^{3}H]L-leucine has been demonstrated in a filter binding assay and in a flashplate assay format. The inventors believe that labelled amino acids but also other compounds, with affinities preferably below 500 nM in the binding assay can be used as replacements of gabapentin.

With regard to the label, several embodiments can be used in the context of the invention. Preferred labels are of course radioactive labels, a list of which is provided further in this specification.

2) Assay formats and conditions

Several assay formats can be used to carry out the method of the present invention. Preferred assay formats include scintillation assays such as the scintillation proximity assay (SPA) or the flashplate assay. Other assay formats well known to those skilled in the arts such as the filter binding assay and the centrifugation assay are also contemplated in the present invention.

SPA and flashplate assays are preferred assay formats for the present invention. Additional details on these assays are provided below.

Scintillation assay format

Scintillation assays technology either involves the use of scintillant beads (for the SPA assay) or plates (for the flashplate assay). SPA beads are usually made from either cerium-doped yttrium ion silicate (y2SiO5:Ce) or polyvinyltoluene (PVT) containing an organic scintillant such as PPO. Flashplates commonly used are those such as Ni chelate flashplates although other flashplates can also be used, such as the Wheat Germ lectin flashplate.

Assays are usually carried out in aqueous buffers using radioisotopes such as ^{3}H, ^{125}I, ^{14}C, ^{35}S or ^{33}P that emit low-energy radiation, the energy of which is easily dissipated in an aqueous environment. For example, the electrons emitted by ^{3}H have an average energy of only 6 keV and have a very short path length (-1 ~tm) in water. If a molecule labelled with one of these isotopes is bound to the bead or flashplate surface, either directly or via interaction with another molecule previously coupled to the bead or flashplate, the emitted radiation will activate the scintillant and produce light. The amount of light produced, which is proportional to the amount of labelled molecules bound to the beads, can be measured conveniently with a liquid scintillation (LS) counter. If the labelled molecule is not attached to the bead or a flashplate surface, its radiation energy is absorbed by the surrounding aqueous solvent before it reaches the bead, and no light is produced. Thus, bound ligands give a scintillation signal, but free ligands do not, and the need for a time- consuming separation step, characteristic of conventional radioligand binding assays, is eliminated. The manipulations required in the assays are reduced to a few simple pipetting steps leading to better precision and reproducibility.

The conditions under which SPA and flashplate assays are performed in the context of the present invention are provided below.

Scintillation assay conditions

a) SPA assay

The SPA assays is first developed to optimize the conditions under which the radioligand binds the secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide. The parameters which can be varied to optimize radioligand binding in a typical SPA assay using Amersham beads include assay temperature, $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide interaction with the radioligand and the SPA beads, radioligand concentration as well as pH variations.

The temperature at which the assay can be carried out can vary from 1 to 30°C. Preferred temperatures range from 18 to 23°C, with 21°C being the most preferred temperature. The interaction of the $\alpha_2\delta$ subunit polypeptide with the SPA beads can be optimized by adjusting the concentration of the polypeptide and by introducing a reagent which will favor this interaction. When 50 mg of Amersham SPA beads are used, the $\alpha_2\delta$-1 subunit polypeptide concentration may vary from 0.1 to 10 pmoles per well, with the optimal concentration being generally around 5 to 6 pmoles per well.

As for the reagent favoring the interaction between the secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide and the radioligand as well as the Amersham SPA beads, the inventors found that imidazole could be efficiently used for that purpose when the $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide is tagged with an amino acid sequence including 6 histidine residues. Furthermore, and more importantly, it was found that imidazole also enhanced binding of the radioligand to the $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 polypeptide.

The concentration of the radioligand is evaluated with respect to the concentration of secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide present in the assay medium. Generally, the concentration of radioligand varies from 1 nM to 100 nM. A preferred [^{3}H]gabapentin concentration is about 5 to 20 nM, with a most preferred concentration being about 10 nM. A preferred [^{3}H]leucine concentration is also about 5 to 20 nM, with a most preferred concentration being about 10 nM. It is to be noted that the concentration of other radioligands having affinities similar to those of [^{3}H]gabapentin and [^{3}H]leucine should also be in the range of about 5 to 20 nM.

Once the optimal radioligand binding conditions have been determined, a test ligand can be introduced in the assay medium to evaluate the level of displacement of the radioligand. The concentration of test ligand to be introduced in the assay medium usually varies from 0.1 nM to about 100 µM. A preferred test ligand concentration of about 10 µM is usually a starting point in a high throughput screening assay. Then, depending on the number of hits obtained, it may be lowered or increased.

It is to be noted that the parameters set forth above, which have been evaluated for a typical SPA assay using Amersham SPA beads can be adjusted by the skilled person, for example if SPA beads of a different type are used.

b) Flashplate assay

Similarly to the SPA assays, the flashplate can first be developed in order to optimize the conditions under which the radioligand binds the $\alpha_2\delta$ subunit polypeptide. The parameters which can be varied to optimize radioligand binding in a typical flashplate assay using NEN Ni chelate flashplates or the Wheat Germ lectin flashplates also include assay temperature, secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide interaction with both the radioligand and the flashplates, radioligand concentration as well as pH variations.

The temperature at which the assay can be carried out can vary from 1 to 30°C. Preferred temperatures range from 18 to 23°C, with 21°C being the most preferred temperature.

The interaction of the secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide with the flashplates can be optimized by adjusting the concentration of the polypeptide and by introducing a reagent which will favor this interaction. When a standard NEN Ni chelate flashplate is used, the secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide volume usually varies between 0.5 and 20 ul for a concentration of secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide of 0.6 pmol/µl. As the published maximum binding capacity of NEN p plates is about 6 pmol per well, the inventors consider that an optimal concentration of secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide is probably around 5 pmol per well at 8 µl.

With regard to the reagent favoring the interaction between the secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide and the radioligand as well as the flashplates, the inventors believe that imidazole could also be efficiently used for that purpose when the secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide is tagged with an amino acid sequence including 6 histidine residues. The inventors also believe that imidazole concentrations can substantially enhanced binding of the radioligand to the secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 polypeptide. The optimal concentration of imidazole used to enhance radioligand binding varies depending on the concentration of secreted soluble $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide used in the assay. For instance, when the volume of the $\alpha_2\delta$-1 subunit polypeptide is about 10 µl ($\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 polypeptide concentration of 0.6 pmol/µl), the optimal imidazole concentration can vary between 1 and 20 mM, with a concentration of about 10 mM being preferred. As mentioned previously, other compounds such as histidine as well as pH variations may be used to enhance radioligand binding.

The concentration of the radioligand is evaluated with respect to the concentration of $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4 subunit polypeptide present in the assay medium. Generally, the concentration of radioligand varies from 1 nM to 100 nM. A preferred [^{3}H]gabapentin concentration is about 5 to 20 nM, with a most preferred concentration being about 10 nM. A preferred [^{3}H]leucine concentration is also about 5 to 20 nM, with a most preferred concentration being about 10 nM. It is to be noted that the concentration of other radioligands having affinities similar to those of [^{3}H]gabapentin and [^{3}H]leucine should also be in the range of about 5 to 20 nM.

Once the optimal radioligand binding conditions have been determined, a test ligand can be introduced in the assay medium to evaluate the level of displacement of the radioligand. The concentration of test ligand to be introduced in the assay medium usually varies from 0.1 nM to about 100 µM. A preferred test ligand concentration of about 10 µM is usually a starting point in a high throughput screening assay. Then, depending on the number of hits obtained, it may be lowered or increased.

The inventors have tested the displacement of a particular radioligand, [^{3}H]gabapentin, with (S+)-3-isobutly gaba. The data provided in the examples which follow clearly shows that the assay can be used in high throughput competition studies.

The invention also resides in a product or ligand isolated, identified or selected using the above screening methods or kits, for use as a medicament or as a lead for further drug development purposes. As indicated above, the compounds are potentially useful for treating disorders of the nervous system, including epilepsy, pain and anxiety.

Further aspects and advantages of the present invention will be described in the following examples, which should be regarded as illustrative and not limiting the scope of the present application.

EXAMPLES

Example 1

Construction of a nucleotide sequence encoding a soluble secreted human $\alpha_2\delta$-2 subunit polypeptide deletion mutant of SEQ ID N°23

a) Primer design

PCR primers were designed to generate the secreted soluble human $\alpha_2\delta$-2 deletion mutant of SEQ ID N° 23 as follows:

5' PCR primer: This was designed to engineer in a KOZAK translation initiation consensus sequence prior to the coding sequence (Kozak *JBC* **266** 19867-19870)

3' PCR primer: This was designed to engineer in six histidine residues followed by a stop-codon at the desired location in the coding sequence. In addition to the stop codon the $\alpha_2\delta$-2 primers also included an *Eco* RI restriction site.

The bold region in each primer sequence denotes the 'tagged' region; addition of sequences not present in the template. Primers were custom synthesized by Perkin Elmer Applied Biosystems UK to the ABI ready pure grade, supplied lyophilized then resuspended to 15μM in 10mM TE. JB197 and 198 were provided with 5' phosphate groups:

5' Primer JB197 (5'-**TCGCCACCATGGCGGTGCCGGCTC**-3', SEQ ID N°25)

3' Primer JB198 (5'-
TCGGAATTCCTCAGTGATGGTGATGGTGATGGGCCCCGCGGCCACAGTC-3', SEQ ID N°26)

b) Protocol for PCR mediated 5' Kozak and 3' 6His tagging of human $\alpha_2\delta$-2

The full length human $\alpha_2\delta$-2 gene (Gen Bank Accession Number AF042792) in a pcDNA 3 vector as described in Brown, J.P. and Gee,N.S., (Cloning and deletion mutagenesis of the α2δ calcium channel subunit from porcine cerebral cortex, *The journal of biological chemistry*, **273**(39):25458-25465) was used as the template in the following PCR reaction.

The reagents were added in the following order in triplicate to a 96 well PCR plate:

		µl
	10x Pfx Amplification buffer	*5*
	10mM dNTPs	*1.5*
	50mM $MgSO_4$	1
5	15µM JB197	1.5
	15µM JB198	1.5
	100ng/µl pcDNA3.1-humans-$\alpha_2\delta$-2	1
	10x PCR Enhancer	5
	H_2O	32.7
10	*2.5 UNITS/µL* PFX *POLYMERASE*	*0.8µL*

The plate was the cycled on an MJ Tetrad DNA engine according to the following cycling conditions:

15 94°C / 2mins

followed by:

for 30 cycles 94°C / 45sec
58°C / 45sec
68°C / 4mins

20 *followed by:*
68°C / 10mins
followed by:
hold at 4°C

25 The 3366bp product was then gel purified from a 1% TAE agarose gel using QIAEX beads and eluted in approximately 50µl TE.

Example 2

Cloning of the PCR fragments of Example 1 into the Baculovirus transfer vector

30 **pFastBac1**

The PCR products of Example 1 were cloned into *Stu* I digested, calf intestinal phosphatase dephosphorylated, phenol chloroform extracted and QIAEX gel purified pFastBac1 (Life Technologies) using the Rapid DNA ligation kit (Roche Diagnostics) transforming XL1-blue ($\alpha_2\delta$-1b) *E. Coli* cells:

35

a) Screening for positive recombinants

Given that the PCR product was cloned by blunt-end ligation a screen was required to select a recombinant with the gene ligated in the positive orientation with respect to the polyhedrin promoter in pFastBac1. This was achieved by restriction digest of miniprep DNA (Qiagen miniprep kit) prepared from colony minicultures and analysis on a 1% TAE agarose gel. A positive clone was identified according to the following digest patterns:

SEQ ID N° 23 in pFastBac1

Eco RI digest performed on miniprep DNA

	Predicted fragments (bp)
PCR product cloned in a positive orientation	4773 and 3368
PCR product cloned in a negative orientation	8127 and 14

b) Sequencing analysis of selected clones

One positive was selected for this clone and used to prepare a plasmid DNA stock of the desired construct (QIAGEN maxi kit). Confirmatory sequence reactions were performed using the Big Dye terminator sequencing kit and run on an ABI 310 Prism Genetic Analyzer. Sequence analysis of both coding strands was performed using a selection of sequencing oligonucleotide primers.

Example 3

Protocol for establishing baculovirus banks for the expression of the $\alpha_2\delta$–2 deletion mutant SEQ ID N°23

Essentially, the protocol used to generate the baculovirus banks is that outlined in the Life Technologies Bac-to Bac™ baculovirus expression systems manual.

a) Transposition of DH10Bac *E Coli* cells

One ng (5µl) of the recombinant pFastBac-1 construct containing the nucleotide sequence encoding the porcine $\alpha_2\delta$-2 deletion mutant of SEQ ID N°23 was added to 100µl of DH10Bac cells thawed on ice. The cells were then mixed gently by tapping the tube then incubated on ice for 30 minutes before heat shock treatment by incubation in a 42°C water bath for 45 seconds. The mixture was then chilled on ice for 2 minutes before the addition of 900µl of S.O.C. medium. The mixture was then placed in a shaking incubator (200rpm) at 37°C for 4hours. The cells were then serially diluted (10 fold dilutions from 10^{-1} to 10^{-3}) and 10µl of each dilution plated on LB agar plates containing

50μg/ml kanamycin, 7μg/ml gentamicin, 10μg/ml tetracycline, 100μg/ml Bluo-gal and 40μg/ml IPTG. The plates were incubated at 37°C for between 1 and 3 days until discrete colonies of blue and white colour were discernible.

b) Isolation of recombinant DNA

White colonies (containing the recombinant bacmid) were picked and grown for 24 hours (to stationary phase) at 37°C with shaking (200rpm) in 2ml of LB containing 50μg/ml kanamycin, 7μg/ml gentamicin and 10μg/ml tetracycline. 1.5ml of culture was then transferred to a microfuge tube and centrifuged at 14,000xg for 1minute. The supernatant was removed and the cells resuspended gently in 0.3ml of 15mM Tris-HCl (pH8.0), 10mM EDTA, 100μg/ml RNase A. 0.3ml of 0.2N NaOH, 1% SDS was then added and the mixture mixed gently before incubation at 22°C for 5 minutes. Then 0.3ml of 3M Potassium acetate (pH5.5) was added and the sample placed on ice for 10 minutes. After centrifugation at 14,000xg for 10 minutes the supernatant was transferred to a tube containing 0.8ml of isopropanol, mixed then placed on ice for 10 minutes before centrifugation at 14,000xg for 10 minutes. The supernatant was then discarded and the pellet rinsed with 0.5ml of 70% ethanol before centrifugation at 14,000xg for 5 minutes. This 70% ethanol rinse was then repeated before removing all of the supernatant and air drying the pellet for 10minutes at room temperature. The pellet was finally resuspended in 40μl of TE.

c) Transfection of sf9 cells with the recombinant bacmid DNA

A 6-well tissue culture plate was seeded with $0.9x10^6$ sf9 cells (cells at log phase having grown from a culture passaged at $0.3x10^6$ cells/ml) per 35mm well in 2ml of Sf-900 II SFM media containing 50units/ml penicillin and 50μg/ml streptomycin. Cells were left to attach at 27°C for 1 hour. Bacmid DNA prepared as described above (5μl) was added to 200μl of Sf-900 II SFM media containing 6μl of CELLFECTIN and mixed before incubation at room temperature for 45 minutes. The cells were washed once with 2ml of Sf-900 II SFM media without antibiotics then 0.8ml of Sf-900 II SFM media was added to each tube containing the lipid-DNA complex. The wash buffer was removed from the cells and the 1ml of diluted lipid-DNA complex overlaid on the cells. The cells were incubated for 5hours at 27°C after which time the transfection mixture was removed and 2ml of Sf-900 II SFM media containing 50units/ml penicillin and 50μg/ml streptomycin was added. The cells were then incubated for 72 hours.

After incubation for 72 hours the media was removed from the cells and centrifuged at 500xg for 5 minutes. The supernatant was then transferred to a fresh tube, this was

labelled as the P0 bank and stored at 4°C in the dark. The P1 bank was prepared by passaging sf9 cells at approx $5x10^6$ cells/ml to $2x10^6$ cells/ml (100ml in a 250ml Erlenmeyer flask) and adding 0.5ml of the P0 bank harvested above. The cells were then incubated shaking (200rpm) at 27°C for 4 days. Under sterile conditions the culture was centrifuged at 500xg for 10 minutes and the supernatant 0.2µM filtered (P1 bank). The P2 bank was prepared by adding 2ml of P1 bank per 400ml culture (in 1L Erlenmeyer flasks) passaged as above to $2x10^6$cells/ml. The culture was incubated as before for 4 days and the supernatant harvested and filtered as described for the P1 bank. The supernatant was first pooled then aliquoted (10ml) and stored at 4°C.

Example 4

Expression of the $\alpha_2\delta$-2 deletion mutant of SEQ ID N°23

To sf9 cells passaged from ~$5x10^6$ cells/ml to 2x106 cells/ml in Sf-900 II SFM media was added 0.1ml virus per 100ml of cells of the appropriate viral bank (400ml volumes in 1L Erlenmeyer flasks). The cells were then cultured for 4-5 days at 27°C with 110rpm shaking. Expression of the protein was confirmed by SDS-PAGE and Western blotting using an anti penta-His monoclonal antibody (Qiagen) and was detected in the culture supernatant and cell lysate.

Example 5

Purification of $\alpha_2\delta$-2deletion mutant of SEQ ID N°23

The-$\alpha_2\delta$-2 deletion mutant of SEQ ID N°23 was purified from the cell lysate following the purification strategy outlined below:

The culture was centrifuged at 6,000xg for 10 minutes and the supernatant removed. The weight of the cell pellet was determined before re-suspension in 20mM Tris pH8.0, 100mMKCl, 1% P40-Nonidet (100ml per 20g of wet cells). A protease inhibitor cocktail (Sigma, Cat# P8849), 1ml/L, was added to the mixture. The solution was then stirred for 10 minutes before centrifugation for 1hour at 30,000xg and 4°C. The supernatant was concentrated (30kDa cut off) to approx. ~300ml then centrifuged for 1hour at 100,000xg.

Supernatant containing the soluble proteins was diluted 1:3 in 10mM Tris-HCl pH8.0 (equilibration buffer) and loaded onto a pre-equilibrated Q-Sepharose column (2.5cm i.d. x 30cm h.) at a flow rate of 900ml/h. After washing with equilibration buffer until a stable A_{280nm} baseline had been achieved, protein was eluted with 20mM Tris-HCl pH8.0, 0.5M KCl, 10mM Imidazole.

The eluate was then loaded onto a Ni-NTA (Qiagen) column (2.5cm i.d. x 6cm h.) pre-equilibrated in 20mM Tris pH8.0, 0.5M KCl, 10mM Imidazole at a flow rate of 2 ml/min. The column was washed successively with buffer A (20mM Tris pH8.0, 0.5M KCl, 20mM Imidazole), buffer B (100mM Tris-HCl pH8.0, 1M KCl), and buffer A again. Elution was performed with buffer C (20mM Tris-HCl pH8.0, 100mM KCl, 0.5M Imidazole). The Ni-NTA eluate (~50ml) was concentrated (30kDa cut-off) to ~2ml and applied at 1ml/min and in 0.2ml aliquots, to an FPLC Superdex-200 column equilibrated in 10mM HEPES, pH7.4, 150mM NaCl. Fractions containing the polypeptide of SEQ ID N°23 were pulled.

Example 6

SPA assay of [^{3}H]gabapentin binding to the secreted soluble human $\alpha_2\delta$-2 subunit of SEQ ID N°23

The assay is carried out at 21°C. Assay components are added in the following order (all reagents are diluted in 10mM HEPES (pH 7.4 at 21°C) to 96-well Optiplates:

25µl	imidazole at various concentrations (diluted from a 1M stock pH8.0, see assay details)
50µl	10mM HEPES pH 7.4
25µl	(50mg) SPA beads (Amersham)
100µl	s-$\alpha_2\delta$-2 subunit polypeptide of SEQ ID No 23 (2µl protein diluted to 100µl)
25µl	radioligand ([^{3}H]gabapentin obtained from example 5

Immediately after adding radioligand, the optiplates were loaded in the Packard Top Count scintillation counter to follow the binding time course. Imidazole was first used in the assay to optimize the specific interaction of the protein's 6His tag with the SPA bead. Imidazole itself (up to 100mM) in the filtration assay has no effect on [^{3}H]gabapentin binding (n=1).

Example 7

Ni Flashplate assay of [^{3}H]gabapentin binding to secreted soluble human $\alpha_2\delta$-2 (SEQ ID N°23)

Assays are carried out at 21°C in a final volume of 250µl in 96-well NEN Ni chelate flash plates. Assay components are added in the following order (all reagents were diluted in 10mM HEPES (pH 7.4 at 21°C)):

25µl 10mM HEPES pH7.4

25µl imidazole at various concentrations (diluted from a 1M stock pH8.0, see assay details)

75µl 10mM HEPES pH 7.4

100µl s-$\alpha_2\delta$-2-6His (2µl protein diluted to 100µl) obtained from example 5

25µl radioligand ([^{3}H]gabapentin (65Ci/mmole)

Immediately after adding the radioligand, flash plates are loaded in the Packard Top Count scintillation counter to follow the binding time course. The '[^{3}H] flash plate' programme (cpm) is used to monitor activity. Imidazole is first used in the assay to optimize the specific interaction of the protein's 6His tag with the Ni flashplate.

Example 8

Ni Flashplate assay of [^{3}H]Leucine binding to secreted soluble human $\alpha_2\delta$-2-6His

The procedure described in example 7 is repeated, except that [^{3}H]gabapentin is replaced by 25 µl (10.1 nM) of [^{3}H]Leucine (141 Ci/mmole).

Example 9

Ni Flashplate assay studying competitive binding of [^{3}H]gabapentin and (S+)-3-isobutyl GABA to human $\alpha_2\delta$-2-6His (SEQ ID N°23).

Assays are carried out at 21°C in a final volume of 250µl in 96-well NEN Ni chelate flash plates. Wells are set up for both 'total' and 'non-specific' binding. Specific binding is defined as that remaining after subtraction of the average of the 'non-specific binding' values from the average of the 'total' binding values. Assay components are added in the following order (all reagents were diluted in 10mM HEPES (pH 7.4 at 21°C)):

25µl 10mM HEPES pH7.4 or 25 µl of the test compound at the appropriate concentration in HEPES

	25µl	200 mM imidazole (diluted from a 1M stock pH8.0, see assay details)
Total binding	75µl	10mM HEPES pH 7.4
Non-specific binding	50µl	10mM HEPES pH 7.4 and 25µl 100µM (S+)-3-isobutyl GABA
	100µl	$\alpha_2\delta$-2-6His (2µl protein* diluted to 100µl)
	25µl	radioligand ([^{3}H]gabapentin or [^{3}H]Leucine)

* The source of $\alpha_2\delta$-2-6His is that purified by fplc Superdex-200 gel filtration (see example 5)

Immediately after adding radioligand, flash plates are loaded in the Packard Top Count scintillation counter to follow the binding time course. Incubation time before the assay is 3 hours. The '[^{3}H] flash plate' programme (cpm) is used to monitor activity

Competition studies are compared across the flash-plate and filter binding methodologies in order to validate the new assay technology with the established filter binding methodology.

GraphPad Prism software is used to process competition curve data and determine IC_{50} and hill slope values. Twelve point competition curves with half log dilution steps of test compounds are used in the experiments.

Example 10

Filter binding assay of [^{3}H]gabapentin binding to the recombinant polypeptide of SEQ ID N°23

Assays were carried out at 21°C in a final volume of 250µl in 96-deep well plates. Assay components were (all reagents were diluted in 10mM HEPES (pH 7.4 at 21°C)):

25µl	compound to test
200µl	Polypeptide of SEQ ID N°23 (3µl protein diluted to 200µl)
25µl	radioligand ([^{3}H]gabapentin (65Ci/mmole)

Plates were incubated at room temperature for 1h prior to filtering on to 96-well GF/B Unifilter plates pre-soaked in 0.3% polyethylenimine. Filters were washed with 3x1ml 50mM Tris-HCl (pH 7.4 at 4°C), and dried over-night. Scintillant (Microscint O, 50µl) was added and the plates counted using a Packard Top Count scintillation counter. Specific binding was ~98% of the 'total' value. In [^{3}H]gabapentin saturation studies, the K_D (nM) obtained was about 10.62.

[^{3}H]Gabapentin saturation studies.

Data shown represent the mean ± SEM determined in 3 separate experiments. Saturation experiments were performed with 12 duplicate data points, [^{3}H]gabapentin concentration ranged from ~1-350nM. data was analysed using KEL-RADLIG

Human s-$\alpha_2\delta$-2-6His

K_D in the filtration assay 28.55 ± 3.08nM

Table 2

Binding affinities of key compounds in the [^{3}H]gabapentin binding assay using s-$\alpha_2\delta$-2-6His

Compound	Ki (nM) and range (n=3) Filtration assay
Gabapentin	*20 (19-23)*
(S+)-3-isobutyl GABA	11 (9.5-13)
(R-)-3-isobutyl GABA	296 (282-310)

N.B. $Ki=IC_{50} / (1+[L]/K_D)$

Competition curves were generated with 10 duplicate data points from 10μM to 1nM and analyzed on GraphPad prism.

Example 11

Binding of [^{3}H]gabapentin to the recombinant polypeptide of SEQ ID N°23 using various flasplates assay formats and conditions

a) Preparation of protein stocks:

Protein was expressed as described in Example 4 except that the cells were infected at $1x10^6$ cells/ml. Additionally, the cells were cultured in 20 litre Applikon fermentation vessels (18L culture volume). The culture was maintained at 27°C and 60% dO2 (100% dO_2 equates to [O_2] when media - without cells - has been saturated with air at 27°C) with single marine impeller stirring at 125rpm. The protein was expressed in either Sf-900 II SFM (LTI Inc) or ESF-921 (Expression Systems Inc.) media.

b) Purification of s-$\alpha_2\delta$-2-6His protein from cell culture supernatants:

On the harvest day (day 4-7 post-infection with virus) the cell culture was centrifuged at 9,000xg for 20 minutes to remove the cellular debris, and the supernatant concentrated to approximately 3 litres using a pellicon tangential-flow filtration system employing 10kDa cut-off cassettes. The concentrated sample was re-centrifuged at 9,000xg for 20 minutes then diluted with 2 volumes of 10mM Tris pH9.0. The diluted sample was then loaded at 10ml/min onto a Q-sepharose column (5cm i.d. x 50cm h.) which was washed with 20mM Tris-HCl (pH8.0) and eluted with 20mM Tris-HCl (pH8.0), 0.5M KCl, 10mM Imidazole.

The eluate was then loaded at 10ml/min onto a Ni-superflow (Qiagen) column (2.5cm i.d. x 6cm h.) pre-equilibrated in 20mM Tris (pH8.0), 0.1M KCl, 10mM Imidazole. The column was washed successively with buffer A (20mM Tris pH8.0, 0.5M KCl, 20mM Imidazole), 20mM Tris-HCl (pH8.0), 100mM KCl, and buffer A again at 10ml/min. Elution was performed with a gradient of buffer C (20mM Tris-HCl (pH8.0), 100mM KCl, 0.5M Imidazole) against buffer B at 2ml/min. Fractions from the gradient elution were assayed for [^{3}H]gabapentin binding activity and the active fractions pooled then dialysed at 4°C four times (each for 24 hours) against 10mM HEPES, 150mM NaCl at a ratio of 1:60 (sample:dialysate). The dialysed material was then aliquoted and frozen for use in the assays as described below.

c) Preparation of protein cocktails for filter, wheat germ lectin and Ni chelate assays

(volumes in µl):

cocktail	x1		x23	
	s-$\alpha_2\delta$-2-6His	HBS	s-$\alpha_2\delta$-2-6His	HBS
0µl	0	75	0	1,725
1µl	1	74	23	1,702
2µl	2	73	46	1,679
4µl	4	71	92	1,633

s-$\alpha_2\delta$-2-6His protein was sourced from the aliquots generated above.

d) Filter and Wheat Germ Lectin flashplate assays

The reagents were added in the following order to each well of either a 96-well Wheat Germ Lectin flashplate or a 96-deep well plate. Conditions were prepared in triplicate for both 'total' and 'non-specific' binding (20µl H_2O added for total binding and 20µl of

100μM (S+)-3-isobutyl GABA to define non-specific binding) for each of the four volumes of protein tested.

Assay set-up per well:

100μM (S+)-3-isobutyl GABA / H_2O	20μl
*100nM [^{3}H]Gabapentin	20μl
235mM HEPES (pH7.3)	85μl
s-$\alpha_2\delta$-2-6His (0, 1, 2 or 4μl - x23 cocktail)	75μl

* 20μl aliquots of the [^{3}H]gabapentin stock added to each well were counted on a liquid β-scintillation counter (Beckman LS 5000TD) to determine the actual concentration of [^{3}H]gabapentin achieved in each well. For these experiments this value was calculated as 10.8nM.

The Wheat Germ flashplate was then counted under continuous cycling conditions on a Packard Top Count Microplate scintillation counter. The plate was counted on the '[^{3}H]flashplate' programme with a count delay and count time of 1 minute. Data for the wheat germ lectin assay was plotted as 'specific' binding (i.e. 'total' minus 'non-specific binding'), see figure 3.

In the Filter assay, the binding reaction in the deep-well plate was left for 1 hour at 22°C then filtered with three 1ml washes of 4°C 50mM Tris (pH 7.4 at 4°C) onto a 96-well GF/B filter plate pre-soaked for 1 hour in 0.3% Polyethylenemine at 4°C. After leaving at 22°C to dry overnight 45μl of Microscint-O (Packard) was added to each filter well and the plate sealed and counted in the Packard Top Count Microplate Scintillation counter on the '[^{3}H]Microscint' programme with a count delay and count time of 1 minute. The mean of the 'total' and 'non-specific' binding is presented in figure 1.

e) Nickel flashplate assay

2.35x Nickel flashplate buffer:

4.7ml	1M HEPES (pH7.3)
0.118ml	10% BSA (Sigma A7906, Fraction V (98%), Lot 57H1088) in H_2O
1.175ml	0.2M Imidazole pH7.3 (NaOH)
14.007ml	H_2O

Assay set-up per well:

100μM (S+)-3-isobutyl GABA / H_2O	20μl
*100nM [^{3}H]Gabapentin	20μl
2.35x Nickel Flashplate buffer	85μl
s-$\alpha_2\delta$-2-6His (0, 1, 2 or 4μl of the x23 cocktail)	75μl

* 20μl aliquots of the [^{3}H]gabapentin stock added to each well were counted on a liquid β-scintillation counter (Beckman LS5000TD) to determine the actual concentration of [^{3}H]gabapentin reached in the each well. For these experiments this value was calculated as 10.8nM.

The Nickel flashplate was then counted under continuous cycling conditions on the Packard Top Count Microplate scintillation counter. The plate was counted on the '[^{3}H]flashplate' programme with a count delay and count time of 1 minute (Figure 2).

The data described demonstrates that it is possible to assay [^{3}H]gabapentin binding to recombinantly expressed freely soluble and purified s-$\alpha_2\delta$-2-6His in either a filter assay or an homogenous flashplate assay in either the Nickel chelate or the Wheat germ lectin format. The data demonstrates the extended stability of the flashplate assay over time, which is crucial if the assay format is to be used for mass-screening purposes, thus enabling the stacking of plates into counters (ideally with appropriate controls on each plate along with test compound wells in order to confirm signal stability across individual plates).

The data presented also demonstrate that it is possible to use the Wheat Germ lectin flashplate assay, as a primary assay or as a secondary screen to further refine and screen ligands identified or selected using the Ni flashplate assay or another format of this invention.

Example 12

Construction of a nucleotide sequence encoding a soluble secreted mouse $\alpha_2\delta$-3 deletion mutant of SEQ ID N°24 as follows.

a) Primer design

PCR primers were designed to generate the secreted soluble mouse $\alpha_2\delta$-3 deletion mutant of SEQ ID N° 24 as follows:

5' PCR primer: This was designed to engineer in a KOZAK translation initiation consensus sequence prior to the coding sequence (Kozak *JBC* 266 19867-19870)

3' PCR primer: This was designed to engineer in six histidine residues followed by a stop-codon at the desired location in the coding sequence. In addition to the stop codon the $\alpha_2\delta$-3 primers also included an *Eco* RI restriction site.

The bold region in each primer sequence denotes the 'tagged' region; addition of sequences not present in the template. Primers were custom synthesized by Perkin Elmer Applied Biosystems UK to the ABI ready pure grade, supplied lyophilized then resuspended to 15µM in 10mM TE. JB201 and 202 were provided with 5' phosphate groups:

5' Primer JB201 (5'-**TCGCCACC**ATGGCCGGGCCGGGC-3', SEQ ID N°27)

3' Primer JB202 (5'-TCTCAGTGATGGTGATGGTGATGCGATGCACCCCCACACTCTC-3', SEQ ID N°28)

b) Protocol for PCR mediated 5' Kozak and 3' 6His tagging of mouse $\alpha_2\delta$-3

The full length mouse $\alpha_2\delta$-3 gene (Gen Bank Accession number AJ010949) in the pcDNA3 vector as described in Brown, J.P. and Gee, N.S., (Cloning and deletion mutagenesis of the α2δ calcium channel subunit from porcine cerebral cortex, *The journal of biological chemistry*, 273(39):25458-25465) was used as the template in the following PCR reaction.

The reagents were added in the following order in triplicate to a 96 well PCR plate:

	µl
10x Pfx *Amplification buffer*	*5*
10mM dNTPs	*1.5*

50mM $MgSO_4$	1
15µM JB201	1.5
15µM JB202	1.5
100ng/µl pcDNA3-mouse-$\alpha_2\delta$-3	1
10x PCR Enhancer	5
H_2O	32.7
2.5 UNITS/µL PFX POLYMERASE	*0.8µL*

The plate was the cycled on an MJ Tetrad DNA engine according to the following cycling conditions:

94°C / 2mins

followed by:

for 30 cycles 94°C / 45sec
60°C / 45sec
68°C / 4mins

followed by:

68°C / 10mins

followed by:

hold at 4°C

The 3244bp product was then gel purified from a 1% TAE agarose gel using QIAEX beads and eluted in approximately 50µl.

The truncated protein of SEQ ID N°24 was expressed such the procedure of example 2, 3 and 4.

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CLAIMS

1. A calcium channel $\alpha_2\delta$ subunit that is soluble and retain the functional characteristics of the full-length or wild-type $\alpha_2\delta$ subunit from which it derives.
2. A calcium channel $\alpha_2\delta$ subunit according to claim 1 wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is of mammalian origin.
3. A calcium channel $\alpha_2\delta$ subunit according to claim 2 wherein the mammalian origin is a human, a porcine, a rat or a mouse origin.
4. A calcium channel $\alpha_2\delta$ subunit according to claim 3 wherein the mammalian origin is a human origin.
5. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 4, wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is naturally expressed in the cerebral cortical.
6. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 5, wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is voltage-dependent.
7. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 6, wherein the $\alpha_2\delta$ subunit is cleaved.
8. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 7, wherein the $\alpha_2\delta$ subunit is cleaved into separate α_2 and δ peptides.
9. A calcium channel $\alpha_2\delta$ subunit according to claim 8, wherein the α_2 and δ peptides are disulfide-bridged.
10. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 6, wherein the $\alpha_2\delta$ subunit is not cleaved.
11. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 10 characterized in that it is purified or isolated.
12. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 11 characterized in that it is processed as the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is naturally processed.
13. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 12 characterized in that it is producable by the baculovirus/insect cells expression system.
14. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 13 characterized in that it is produced by the baculovirus/insect cells expression system.
15. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 14 characterized in that its δ peptide comprises at least the ligand-interacting part(s) of the complete δ peptide from which it originates
16. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 15 characterized in that its δ peptide has a C-terminal truncation with respect to the complete δ peptide

from which it originates, said truncation being sufficient to render the truncated δ peptide soluble.

17. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 16 characterized in that its α_2 peptide comprises at least the ligand-interacting part(s) of the complete α_2 peptide from which it originates.

18. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 15 or 17 characterized in that ligand is gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine, Spermine or L-Phenylalanine.

19. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 18 characterized in that its α_2 peptide comprises at least the ligand-interacting part(s) of the complete α_2 peptide from which it originates, its δ peptide comprises at least the ligand-interacting part(s) of the complete δ peptide from which it originates and its δ peptide does not comprise a part of the transmembrane domain of the complete δ peptide from which it originates which renders said calcium channel insoluble.

20. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 19 wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates is *$\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4.*

21. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 20 wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°20.

22. A calcium channel $\alpha_2\delta$ subunit according to claim 20 or 21 characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 4, SEQ ID N° 5 or SEQ ID N° 6.

23. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 20 to 22 characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 340 and amino acid number 1062 of SEQ ID N°20.

24. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 20 wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°21.

25. A calcium channel $\alpha_2\delta$ subunit according to claim 20 or 24 characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 10, SEQ ID N° 11 or SEQ ID N° 12.

26. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 20, 24 or 25 characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 306 and amino acid number 1019 of SEQ ID N°20.

27. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 20 wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°55.

28. A calcium channel $\alpha_2\delta$ subunit according to claim 20 or 27 characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 53, SEQ ID N° 54 or SEQ ID N° 55.

29. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 20, 27 or 28 characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 302 and amino acid number 1050 of SEQ ID N°55.

30. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 20 wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°33 or SEQ ID N°44.

31. A calcium channel $\alpha_2\delta$ subunit according to claim 20 or 30 characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 34, SEQ ID N° 35, SEQ ID N° 36, SEQ ID N° 41, SEQ ID N° 42 or SEQ ID N° 43.

32. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 20, 30 or 31 characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 302 and amino acid number 1018 of SEQ ID N°33 or SEQ ID N°44.

33. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 20, 30 or 31 characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 302 and amino acid number 1018 of SEQ ID N°33 or SEQ ID N°44.

34. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 20, 30, 31, 32 or 33 characterized in that its α_2 peptide comprises the region comprised between amino acid number 302 and amino acid number 946 or 997 of SEQ ID N°33 or of SEQ ID N°44 and its δ peptide comprises the region comprised between amino acid number 984 and amino acid number 1018 of SEQ ID N°33 or of SEQ ID N°44.

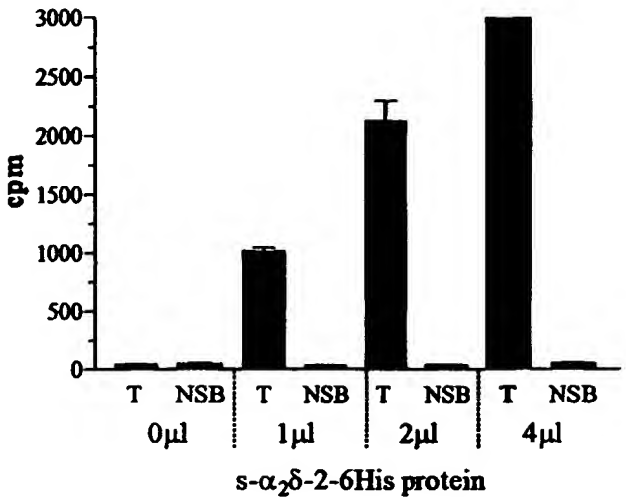
35. A calcium channel $\alpha_2\delta$ subunit characterized in that its α_2 peptide and its δ peptide have 99%, 98%, 97%, 96%, or 95% homology or identity with the α_2 peptide and the δ peptide respectively of a calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 34.

36. A nucleic acid molecule characterized in that its nucleotide sequence comprises a nucleotide sequence which encodes a calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 35.

37. A nucleic acid molecule characterized in that its nucleotide sequence comprises a nucleotide sequence which encodes the α_2 peptide or the δ peptide of a calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 35.
38. A nucleic acid molecule which hybridizes under stringent conditions with a nucleic acid molecule according to claim 36, 37 or 39.
39. A nucleic acid molecule according to any one of claims 36 to 38 which comprises SEQ ID N°1, SEQ ID N°2, SEQ ID N°3, SEQ ID N°7, SEQ ID N°8, SEQ ID N°9, SEQ ID N°13, SEQ ID N°14, SEQ ID N°15, SEQ ID N°30, SEQ ID N°31, SEQ ID N°32, SEQ ID N°38, SEQ ID N°39, SEQ ID N°40, SEQ ID N°50, SEQ ID N°51, or SEQ ID N°52.
40. A vector capable of expressing a nucleic acid molecule according to any one of claims 36 to 39.
41. An expression vector comprising a nucleic acid molecule according to any one of claims 36 to 39.
42. A vector according to claim 40 or 41 which is a baculovirus vector.
43. A cell comprising a nucleic acid molecule according to any one of claims 36 to 39.
44. A cell comprising a vector according to claim 40, 41 or 42.
45. A cell according to claim 43 or 44 which is a mammalian cell or an insect cell.
46. A composition comprising a calcium channel $\alpha_2\delta$ subunit according to any one of claims 7 to 9 and a calcium channel $\alpha_2\delta$ subunit according to claim 10.
47. Screening assay using a calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 35.
48. Screening assay according to claim 47 which is an SPA assay, a Flashplate assay, a Nickel Flasplate assay, a Filter binding assay or a Wheat Germ Lectin flasplate assay.
49. Use of screening assay according to claim 47 or 48 to detect or measure the binding or interaction of a ligand of a calcium channel $\alpha_2\delta$ subunit and a calcium channel $\alpha_2\delta$ subunit.
50. Use according to claim 49 wherein the ligand is gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine, Spermine or L-Phenylalanine.
51. Kit to detect or measure the binding or interaction of a ligand of a calcium channel $\alpha_2\delta$ subunit and a calcium channel $\alpha_2\delta$ subunit comprising a calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 35.
52. Kit according to claim 51 wherein the ligand is gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine, Spermine or L-Phenylalanine.

53. Kit according to claim 51 or 52 usable in an SPA assay, a Flashplate assay, a Nickel Flasplate assay, a Filter binding assay or a Wheat Germ Lectin flasplate assay.

Figure 1



T -Total Binding
NSB -Non-Specific Binding

Figure 2

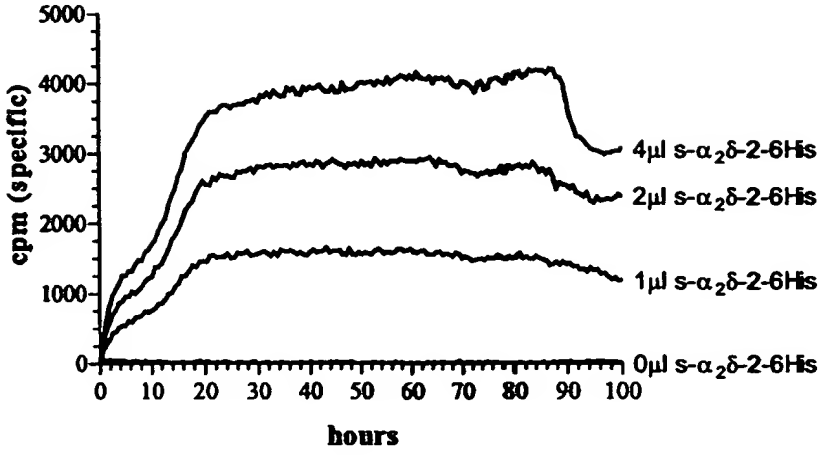
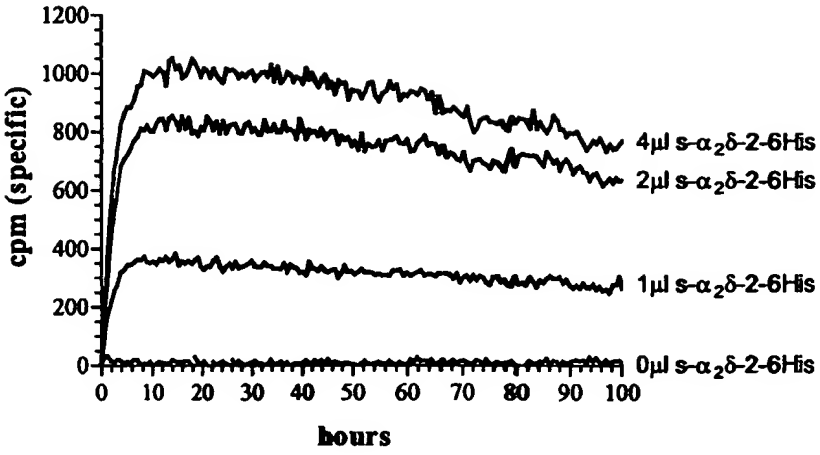


Figure 3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Gln Asn His Gln Trp Asp Gln Val Gly Arg Phe Phe Ser Glu Val Asp
            900                 905                 910

Ala Asn Leu Met Leu Ala Leu Tyr Asn Asn Ser Phe Tyr Thr Arg Lys
        915                 920                 925

Glu Ser Tyr Asp Tyr Gln Ala Ala Cys Ala Pro Gln Pro Pro Gly Asn
    930                 935                 940

Leu Gly Ala Ala Pro Arg Gly Val Phe Val Pro Thr Val Ala Asp Phe
945                 950                 955                 960

Leu Asn Leu Ala Trp Trp Thr Ser Ala Ala Ala Trp Ser Leu Phe Gln
                965                 970                 975

Gln Leu Leu Tyr Gly Leu Ile Tyr His Ser Trp Phe Gln Ala Asp Pro
            980                 985                 990

Ala Glu Ala Glu Gly Ser Pro Glu Thr Arg Glu Ser Ser Cys Val Met
        995                1000                1005

Lys Gln Thr Gln Tyr Tyr Phe Gly Ser Val Asn Ala Ser Tyr Asn Ala
   1010                1015                1020

Ile Ile Asp Cys Gly Asn Cys Ser Arg Leu Phe His Ala Gln Arg Leu
1025                1030                1035                1040

Thr Asn Thr Asn Leu Leu Phe Val Val Ala Glu Lys Pro Leu Cys Ser
                1045                1050                1055

Gln Cys Glu Ala Gly Arg
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            20                  25                  30

Thr Arg Arg Pro Thr Ser Gly Pro Pro Arg Pro Leu Trp Leu Leu Leu
        35                  40                  45

Pro Leu Leu Pro Leu Leu Ala Ala Pro Gly Ala Ser Ala Tyr Ser Phe
    50                  55                  60

Pro Gln Gln His Thr Met Gln His Trp Ala Arg Arg Leu Glu Gln Glu
65                  70                  75                  80

Val Asp Gly Val Met Arg Ile Phe Gly Gly Val Gln Gln Leu Arg Glu
                85                  90                  95

Ile Tyr Lys Asp Asn Arg Asn Leu Phe Glu Val Gln Glu Asn Glu Pro
            100                 105                 110

Gln Lys Leu Val Glu Lys Val Ala Gly Asp Ile Glu Ser Leu Leu Asp
        115                 120                 125

Arg Lys Val Gln Ala Leu Lys Arg Leu Ala Asp Ala Ala Glu Asn Phe
    130                 135                 140

Gln Lys Ala His Arg Trp Gln Asp Asn Ile Lys Glu Glu Asp Ile Val
145                 150                 155                 160

Tyr Tyr Asp Ala Lys Ala Asp Ala Glu Leu Asp Asp Pro Glu Ser Glu
                165                 170                 175

Asp Val Glu Arg Gly Ser Lys Ala Ser Thr Leu Arg Leu Asp Phe Ile
            180                 185                 190

Glu Asp Pro Asn Phe Lys Asn Lys Val Asn Tyr Ser Tyr Ala Ala Val
        195                 200                 205

Gln Ile Pro Thr Asp Ile Tyr Lys Gly Ser Thr Val Ile Leu Asn Glu
    210                 215                 220

Leu Asn Trp Thr Glu Ala Leu Glu Asn Val Phe Met Glu Asn Arg Arg
225                 230                 235                 240

Gln Asp Pro Thr Leu Leu Trp Gln Val Phe Gly Ser Ala Thr Gly Val
                245                 250                 255

Thr Arg Tyr Tyr Pro Ala Thr Pro Trp Arg Ala Pro Lys Lys Ile Asp
            260                 265                 270

Leu Tyr Asp Val Arg Arg Arg Pro Trp Tyr Ile Gln Gly Ala Ser Ser
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        275                 280                 285

Pro Lys Asp Met Val Ile Ile Val Asp Val Ser Gly Ser Val Ser Gly
    290                 295                 300

Leu Thr Leu Lys Leu Met Lys Thr Ser Val Cys Glu Met Leu Asp Thr
305                 310                 315                 320

Leu Ser Asp Asp Asp Tyr Val Asn Val Ala Ser Phe Asn Glu Lys Ala
                325                 330                 335

Gln Pro Val Ser Cys Phe Thr His Leu Val Gln Ala Asn Val Arg Asn
            340                 345                 350

Lys Lys Val Phe Lys Glu Ala Val Gln Gly Met Val Ala Lys Gly Thr
        355                 360                 365

Thr Gly Tyr Lys Ala Gly Phe Glu Tyr Ala Phe Asp Gln Leu Gln Asn
    370                 375                 380

Ser Asn Ile Thr Arg Ala Asn Cys Asn Lys Met Ile Met Met Phe Thr
385                 390                 395                 400

Asp Gly Gly Glu Asp Arg Val Gln Asp Val Phe Glu Lys Tyr Asn Trp
                405                 410                 415

Pro Asn Arg Thr Val Arg Val Phe Thr Phe Ser Val Gly Gln His Asn
            420                 425                 430

Tyr Asp Val Thr Pro Leu Gln Trp Met Ala Cys Ala Asn Lys Gly Tyr
        435                 440                 445

Tyr Phe Glu Ile Pro Ser Ile Gly Ala Ile Arg Ile Asn Thr Gln Glu
    450                 455                 460

Tyr Leu Asp Val Leu Gly Arg Pro Met Val Leu Ala Gly Lys Glu Ala
465                 470                 475                 480

Lys Gln Val Gln Trp Thr Asn Val Tyr Glu Asp Ala Leu Gly Leu Gly
                485                 490                 495

Leu Val Val Thr Gly Thr Leu Pro Val Phe Asn Leu Thr Gln Asp Gly
            500                 505                 510

Pro Gly Glu Lys Lys Asn Gln Leu Ile Leu Gly Val Met Gly Ile Asp
        515                 520                 525

Val Ala Leu Asn Asp Ile Lys Arg Leu Thr Pro Asn Tyr Thr Leu Gly
    530                 535                 540

Ala Asn Gly Tyr Val Phe Ala Ile Asp Leu Asn Gly Tyr Val Leu Leu
545                 550                 555                 560

His Pro Asn Leu Lys Pro Gln Thr Thr Asn Phe Arg Glu Pro Val Thr
                565                 570                 575

Leu Asp Phe Leu Asp Ala Glu Leu Glu Asp Glu Asn Lys Glu Glu Ile
            580                 585                 590
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Arg Arg Ser Met Ile Asp Gly Asn Lys Gly His Lys Gln Ile Arg Thr
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Leu Val Lys Ser Leu Asp Glu Arg Tyr Ile Asp Glu Val Thr Arg Asn
610 615 620

Tyr Thr Trp Val Pro Ile Arg Ser Thr Asn Tyr Ser Leu Gly Leu Val
625 630 635 640

Leu Pro Pro Tyr Ser Thr Phe Tyr Leu Gln Ala Asn Leu Ser Asp Gln
645 650 655

Ile Leu Gln Val Lys Tyr Phe Glu Phe Leu Leu Pro Ser Ser Phe Glu
660 665 670

Ser Glu Gly His Val Phe Ile Ala Pro Arg Glu Tyr Cys Lys Asp Leu
675 680 685

Asn Ala Ser Asp Asn Asn Thr Glu Phe Leu Lys Asn Phe Ile Glu Leu
690 695 700

Met Glu Lys Val Thr Pro Asp Ser Lys Gln Cys Asn Asn Phe Leu Leu
705 710 715 720

His Asn Leu Ile Leu Asp Thr Gly Ile Thr Gln Gln Leu Val Glu Arg
725 730 735

Val Trp Arg Asp Gln Asp Leu Asn Thr Tyr Ser Leu Leu Ala Val Phe
740 745 750

Ala Ala Thr Asp Gly Gly Ile Thr Arg Val Phe Pro Asn Lys Ala Ala
755 760 765

Glu Asp Trp Thr Glu Asn Pro Glu Pro Phe Asn Ala Ser Phe Tyr Arg
770 775 780

Arg Ser Leu Asp Asn His Gly Tyr Val Phe Lys Pro Pro His Gln Asp
785 790 795 800

Ala Leu Leu Arg Pro Leu Glu Leu Glu Asn Asp Thr Val Gly Ile Leu
805 810 815

Val Ser Thr Ala Val Glu Leu Ser Leu Gly Arg Arg Thr Leu Arg Pro
820 825 830

Ala Val Val Gly Val Lys Leu Asp Leu Glu Ala Trp Ala Glu Lys Phe
835 840 845

Lys Val Leu Ala Ser Asn Arg Thr His Gln Asp Gln Pro Gln Lys Cys
850 855 860

Gly Pro Asn Ser His Cys Glu Met Asp Cys Glu Val Asn Asn Glu Asp
865 870 875 880

Leu Leu Cys Val Leu Ile Asp Asp Gly Gly Phe Leu Val Leu Ser Asn
885 890 895

Gln Asn His Gln Trp Asp Gln Val Gly Arg Phe Phe Ser Glu Val Asp
900 905 910

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Ala Asn Leu Met Leu Ala Leu Tyr Asn Asn Ser Phe Tyr Thr Arg Lys
        915                 920                 925

Glu Ser Tyr Asp Tyr Gln Ala Ala Cys Ala Pro Gln Pro Pro Gly Asn
    930                 935                 940

Leu Gly Ala Ala Pro Arg Gly Val Phe Val Pro Thr Val Ala Asp Phe
945                 950                 955                 960

Leu Asn Leu Ala Trp Trp Thr Ser Ala Ala Ala Trp Ser Leu Phe Gln
                965                 970                 975

Gln Leu Leu Tyr Gly Leu Ile Tyr His Ser Trp Phe Gln Ala Asp Pro
            980                 985                 990

Ala Glu Ala Glu Gly Ser Pro Glu Thr Arg Glu Ser Ser Cys Val Met
        995                1000                1005

Lys Gln Thr Gln Tyr Tyr Phe Gly Ser Val Asn Ala Ser Tyr Asn Ala
   1010                1015                1020

Ile Ile Asp Cys Gly Asn Cys Ser Arg Leu Phe His Ala Gln Arg Leu
1025                1030                1035                1040

Thr Asn Thr Asn Leu Leu Phe Val Val Ala Glu Lys Pro Leu Cys Ser
                1045                1050                1055

Gln Cys Glu Ala Gly Arg Leu Leu Gln Lys Glu Thr His Cys Pro Ala
            1060                1065                1070

Asp Gly Pro Glu Gln Cys Glu Leu Val Gln
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            20                  25                  30

Thr Arg Arg Pro Thr Ser Gly Pro Pro Arg Pro Leu Trp Leu Leu Leu
        35                  40                  45

Pro Leu Leu Pro Leu Leu Ala Ala Pro Gly Ala Ser Ala Tyr Ser Phe
    50                  55                  60

Pro Gln Gln His Thr Met Gln His Trp Ala Arg Arg Leu Glu Gln Glu
65                  70                  75                  80

Val Asp Gly Val Met Arg Ile Phe Gly Gly Val Gln Gln Leu Arg Glu
                85                  90                  95
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Ile Tyr Lys Asp Asn Arg Asn Leu Phe Glu Val Gln Glu Asn Glu Pro
            100                 105                 110

Gln Lys Leu Val Glu Lys Val Ala Gly Asp Ile Glu Ser Leu Leu Asp
        115                 120                 125

Arg Lys Val Gln Ala Leu Lys Arg Leu Ala Asp Ala Ala Glu Asn Phe
    130                 135                 140

Gln Lys Ala His Arg Trp Gln Asp Asn Ile Lys Glu Glu Asp Ile Val
145                 150                 155                 160

Tyr Tyr Asp Ala Lys Ala Asp Ala Glu Leu Asp Asp Pro Glu Ser Glu
                165                 170                 175

Asp Val Glu Arg Gly Ser Lys Ala Ser Thr Leu Arg Leu Asp Phe Ile
            180                 185                 190

Glu Asp Pro Asn Phe Lys Asn Lys Val Asn Tyr Ser Tyr Ala Ala Val
        195                 200                 205

Gln Ile Pro Thr Asp Ile Tyr Lys Gly Ser Thr Val Ile Leu Asn Glu
    210                 215                 220

Leu Asn Trp Thr Glu Ala Leu Glu Asn Val Phe Met Glu Asn Arg Arg
225                 230                 235                 240

Gln Asp Pro Thr Leu Leu Trp Gln Val Phe Gly Ser Ala Thr Gly Val
                245                 250                 255

Thr Arg Tyr Tyr Pro Ala Thr Pro Trp Arg Ala Pro Lys Lys Ile Asp
            260                 265                 270

Leu Tyr Asp Val Arg Arg Arg Pro Trp Tyr Ile Gln Gly Ala Ser Ser
        275                 280                 285

Pro Lys Asp Met Val Ile Ile Val Asp Val Ser Gly Ser Val Ser Gly
    290                 295                 300

Leu Thr Leu Lys Leu Met Lys Thr Ser Val Cys Glu Met Leu Asp Thr
305                 310                 315                 320

Leu Ser Asp Asp Asp Tyr Val Asn Val Ala Ser Phe Asn Glu Lys Ala
                325                 330                 335

Gln Pro Val Ser Cys Phe Thr His Leu Val Gln Ala Asn Val Arg Asn
            340                 345                 350

Lys Lys Val Phe Lys Glu Ala Val Gln Gly Met Val Ala Lys Gly Thr
        355                 360                 365

Thr Gly Tyr Lys Ala Gly Phe Glu Tyr Ala Phe Asp Gln Leu Gln Asn
    370                 375                 380

Ser Asn Ile Thr Arg Ala Asn Cys Asn Lys Met Ile Met Met Phe Thr
385                 390                 395                 400

Asp Gly Gly Glu Asp Arg Val Gln Asp Val Phe Glu Lys Tyr Asn Trp
                405                 410                 415
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Pro Asn Arg Thr Val Arg Val Phe Thr Phe Ser Val Gly Gln His Asn
            420                 425                 430

Tyr Asp Val Thr Pro Leu Gln Trp Met Ala Cys Ala Asn Lys Gly Tyr
        435                 440                 445

Tyr Phe Glu Ile Pro Ser Ile Gly Ala Ile Arg Ile Asn Thr Gln Glu
    450                 455                 460

Tyr Leu Asp Val Leu Gly Arg Pro Met Val Leu Ala Gly Lys Glu Ala
465                 470                 475                 480

Lys Gln Val Gln Trp Thr Asn Val Tyr Glu Asp Ala Leu Gly Leu Gly
                485                 490                 495

Leu Val Val Thr Gly Thr Leu Pro Val Phe Asn Leu Thr Gln Asp Gly
            500                 505                 510

Pro Gly Glu Lys Lys Asn Gln Leu Ile Leu Gly Val Met Gly Ile Asp
        515                 520                 525

Val Ala Leu Asn Asp Ile Lys Arg Leu Thr Pro Asn Tyr Thr Leu Gly
    530                 535                 540

Ala Asn Gly Tyr Val Phe Ala Ile Asp Leu Asn Gly Tyr Val Leu Leu
545                 550                 555                 560

His Pro Asn Leu Lys Pro Gln Thr Thr Asn Phe Arg Glu Pro Val Thr
                565                 570                 575

Leu Asp Phe Leu Asp Ala Glu Leu Glu Asp Glu Asn Lys Glu Glu Ile
            580                 585                 590

Arg Arg Ser Met Ile Asp Gly Asn Lys Gly His Lys Gln Ile Arg Thr
        595                 600                 605

Leu Val Lys Ser Leu Asp Glu Arg Tyr Ile Asp Glu Val Thr Arg Asn
    610                 615                 620

Tyr Thr Trp Val Pro Ile Arg Ser Thr Asn Tyr Ser Leu Gly Leu Val
625                 630                 635                 640

Leu Pro Pro Tyr Ser Thr Phe Tyr Leu Gln Ala Asn Leu Ser Asp Gln
                645                 650                 655

Ile Leu Gln Val Lys Tyr Phe Glu Phe Leu Leu Pro Ser Ser Phe Glu
            660                 665                 670

Ser Glu Gly His Val Phe Ile Ala Pro Arg Glu Tyr Cys Lys Asp Leu
        675                 680                 685

Asn Ala Ser Asp Asn Asn Thr Glu Phe Leu Lys Asn Phe Ile Glu Leu
    690                 695                 700

Met Glu Lys Val Thr Pro Asp Ser Lys Gln Cys Asn Asn Phe Leu Leu
705                 710                 715                 720

His Asn Leu Ile Leu Asp Thr Gly Ile Thr Gln Gln Leu Val Glu Arg
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                725                 730                 735

Val Trp Arg Asp Gln Asp Leu Asn Thr Tyr Ser Leu Leu Ala Val Phe
            740                 745                 750

Ala Ala Thr Asp Gly Gly Ile Thr Arg Val Phe Pro Asn Lys Ala Ala
        755                 760                 765

Glu Asp Trp Thr Glu Asn Pro Glu Pro Phe Asn Ala Ser Phe Tyr Arg
    770                 775                 780

Arg Ser Leu Asp Asn His Gly Tyr Val Phe Lys Pro Pro His Gln Asp
785                 790                 795                 800

Ala Leu Leu Arg Pro Leu Glu Leu Glu Asn Asp Thr Val Gly Ile Leu
                805                 810                 815

Val Ser Thr Ala Val Glu Leu Ser Leu Gly Arg Arg Thr Leu Arg Pro
            820                 825                 830

Ala Val Val Gly Val Lys Leu Asp Leu Glu Ala Trp Ala Glu Lys Phe
        835                 840                 845

Lys Val Leu Ala Ser Asn Arg Thr His Gln Asp Gln Pro Gln Lys Cys
    850                 855                 860

Gly Pro Asn Ser His Cys Glu Met Asp Cys Glu Val Asn Asn Glu Asp
865                 870                 875                 880

Leu Leu Cys Val Leu Ile Asp Asp Gly Gly Phe Leu Val Leu Ser Asn
                885                 890                 895

Gln Asn His Gln Trp Asp Gln Val Gly Arg Phe Phe Ser Glu Val Asp
            900                 905                 910

Ala Asn Leu Met Leu Ala Leu Tyr Asn Asn Ser Phe Tyr Thr Arg Lys
        915                 920                 925

Glu Ser Tyr Asp Tyr Gln Ala Ala Cys Ala Pro Gln Pro Pro Gly Asn
    930                 935                 940

Leu Gly Ala Ala Pro Arg Gly Val Phe Val Pro Thr Val Ala Asp Phe
945                 950                 955                 960

Leu Asn Leu Ala Trp Trp Thr Ser Ala Ala Ala Trp Ser Leu Phe Gln
                965                 970                 975

Gln Leu Leu Tyr Gly Leu Ile Tyr His Ser Trp Phe Gln Ala Asp Pro
            980                 985                 990

Ala Glu Ala Glu Gly Ser Pro Glu Thr Arg Glu Ser Ser Cys Val Met
        995                1000                1005

Lys Gln Thr Gln Tyr Tyr Phe Gly Ser Val Asn Ala Ser Tyr Asn Ala
   1010                1015                1020

Ile Ile Asp Cys Gly Asn Cys Ser Arg Leu Phe His Ala Gln Arg Leu
1025                1030                1035                1040
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Thr Asn Thr Asn Leu Leu Phe Val Val Ala Glu Lys Pro Leu Cys Ser
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Gln Cys Glu Ala Gly Arg Leu Leu Gln Lys Glu Thr His Cys Pro Ala
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Asp Gly Pro Glu Gln Cys Glu Leu Val Gln Arg Pro Arg Tyr Arg Arg
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<211> 3213
<212> DNA
<213> Homo sapiens

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tccggttccc agcttctgca aaagaaatac aaagagtatg agaaagacgt tgccatagaa 240
gaaattgatg gcctccaact ggtaaagaag ctggcaaaga acatggaaga gatgtttcac 300
aagaagtctg aggccgtcag gcgtctggtg gaggctgcag aagaagcaca cctgaaacat 360
gaatttgatg cagacttaca gtatgaatac ttcaatgctg tgctgataaa tgaaagggac 420
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aagatcagaa gggcccagaa gatcagaagg cgcccagaat cttgtcatgg cttccatcct 3180
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<211> 1019
<212> PRT
<213> Homo sapiens

<400> 10
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Leu Leu Ala Ala Ala Leu Leu Tyr Ala Ala Leu Gly Asp Val Val Arg
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Ser Glu Gln Gln Ile Pro Leu Ser Val Val Lys Leu Trp Ala Ser Ala
35 40 45

Phe Gly Gly Glu Ile Lys Ser Ile Ala Ala Lys Tyr Ser Gly Ser Gln
50 55 60

Leu Leu Gln Lys Lys Tyr Lys Glu Tyr Glu Lys Asp Val Ala Ile Glu
65 70 75 80

Glu Ile Asp Gly Leu Gln Leu Val Lys Lys Leu Ala Lys Asn Met Glu
85 90 95

Glu Met Phe His Lys Lys Ser Glu Ala Val Arg Arg Leu Val Glu Ala
100 105 110

Ala Glu Glu Ala His Leu Lys His Glu Phe Asp Ala Asp Leu Gln Tyr
115 120 125

Glu Tyr Phe Asn Ala Val Leu Ile Asn Glu Arg Asp Lys Asp Gly Asn
130 135 140

Phe Leu Glu Leu Gly Lys Glu Phe Ile Leu Ala Pro Asn Asp His Phe
145 150 155 160

Asn Asn Leu Pro Val Asn Ile Ser Leu Ser Asp Val Gln Val Pro Thr
165 170 175

```
Asn Met Tyr Asn Lys Asp Pro Ala Ile Val Asn Gly Val Tyr Trp Ser
            180                 185                 190

Glu Ser Leu Asn Lys Val Phe Val Asp Asn Phe Asp Arg Asp Pro Ser
        195                 200                 205

Leu Ile Trp Gln Tyr Phe Gly Ser Ala Lys Gly Phe Phe Arg Gln Tyr
    210                 215                 220

Pro Gly Ile Lys Trp Glu Pro Asp Glu Asn Gly Val Ile Ala Phe Asp
225                 230                 235                 240

Cys Arg Asn Arg Lys Trp Tyr Ile Gln Ala Ala Thr Ser Pro Lys Asp
                245                 250                 255

Val Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu Arg Leu
            260                 265                 270

Thr Ile Ala Lys Gln Thr Val Ser Ser Ile Leu Asp Thr Leu Gly Asp
        275                 280                 285

Asp Asp Phe Phe Asn Ile Ile Ala Tyr Asn Glu Glu Leu His Tyr Val
    290                 295                 300

Glu Pro Cys Leu Asn Gly Thr Leu Val Gln Ala Asp Arg Thr Asn Lys
305                 310                 315                 320

Glu His Phe Arg Glu His Leu Asp Lys Leu Phe Ala Lys Gly Ile Gly
                325                 330                 335

Met Leu Asp Ile Ala Leu Asn Glu Ala Phe Asn Ile Leu Ser Asp Phe
            340                 345                 350

Asn His Thr Gly Gln Gly Ser Ile Cys Ser Gln Ala Ile Met Leu Ile
        355                 360                 365

Thr Asp Gly Ala Val Asp Thr Tyr Asp Thr Ile Phe Ala Lys Tyr Asn
    370                 375                 380

Trp Pro Asp Arg Lys Val Arg Ile Phe Thr Tyr Leu Ile Gly Arg Glu
385                 390                 395                 400

Ala Ala Phe Ala Asp Asn Leu Lys Trp Met Ala Cys Ala Asn Lys Gly
                405                 410                 415

Phe Phe Thr Gln Ile Ser Thr Leu Ala Asp Val Gln Glu Asn Val Met
            420                 425                 430

Glu Tyr Leu His Val Leu Ser Arg Pro Lys Val Ile Asp Gln Glu His
        435                 440                 445

Asp Val Val Trp Thr Glu Ala Tyr Ile Asp Ser Thr Leu Thr Asp Asp
    450                 455                 460

Gln Gly Pro Val Leu Met Thr Thr Val Ala Met Pro Val Phe Ser Lys
465                 470                 475                 480

Gln Asn Glu Thr Arg Ser Lys Gly Ile Leu Leu Gly Val Val Gly Thr
                485                 490                 495
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Asp Val Pro Val Lys Glu Leu Leu Lys Thr Ile Pro Lys Tyr Lys Leu
            500                 505                 510

Gly Ile His Gly Tyr Ala Phe Ala Ile Thr Asn Asn Gly Tyr Ile Leu
        515                 520                 525

Thr His Pro Glu Leu Arg Leu Leu Tyr Glu Glu Gly Lys Lys Arg Arg
    530                 535                 540

Lys Pro Asn Tyr Ser Ser Val Asp Leu Ser Glu Val Glu Trp Glu Asp
545                 550                 555                 560

Arg Asp Asp Val Leu Arg Asn Ala Met Val Asn Arg Lys Thr Gly Lys
                565                 570                 575

Phe Ser Met Glu Val Lys Lys Thr Val Asp Lys Gly Lys Arg Val Leu
            580                 585                 590

Val Met Thr Asn Asp Tyr Tyr Tyr Thr Asp Ile Lys Gly Thr Pro Phe
        595                 600                 605

Ser Leu Gly Val Ala Leu Ser Arg Gly His Gly Lys Tyr Phe Phe Arg
    610                 615                 620

Gly Asn Val Thr Ile Glu Glu Gly Leu His Asp Leu Glu His Pro Asp
625                 630                 635                 640

Val Ser Leu Ala Asp Glu Trp Ser Tyr Cys Asn Thr Asp Leu His Pro
                645                 650                 655

Glu His Arg His Leu Ser Gln Leu Glu Ala Ile Lys Leu Tyr Leu Lys
            660                 665                 670

Gly Lys Glu Pro Leu Leu Gln Cys Asp Lys Glu Leu Ile Gln Glu Val
        675                 680                 685

Leu Phe Asp Ala Val Val Ser Ala Pro Ile Glu Ala Tyr Trp Thr Ser
    690                 695                 700

Leu Ala Leu Asn Lys Ser Glu Asn Ser Asp Lys Gly Val Glu Val Ala
705                 710                 715                 720

Phe Leu Gly Thr Arg Thr Gly Leu Ser Arg Ile Asn Leu Phe Val Gly
                725                 730                 735

Ala Glu Gln Leu Thr Asn Gln Asp Phe Leu Lys Ala Gly Asp Lys Glu
            740                 745                 750

Asn Ile Phe Asn Ala Asp His Phe Pro Leu Trp Tyr Arg Arg Ala Ala
        755                 760                 765

Glu Gln Ile Pro Gly Ser Phe Val Tyr Ser Ile Pro Phe Ser Thr Gly
    770                 775                 780

Pro Val Asn Lys Ser Asn Val Val Thr Ala Ser Thr Ser Ile Gln Leu
785                 790                 795                 800

Leu Asp Glu Arg Lys Ser Pro Val Val Ala Ala Val Gly Ile Gln Met
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805 810 815

Lys Leu Glu Phe Phe Gln Arg Lys Phe Trp Thr Ala Ser Arg Gln Cys
820 825 830

Ala Ser Leu Asp Gly Lys Cys Ser Ile Ser Cys Asp Asp Glu Thr Val
835 840 845

Asn Cys Tyr Leu Ile Asp Asn Asn Gly Phe Ile Leu Val Ser Glu Asp
850 855 860

Tyr Thr Gln Thr Gly Asp Phe Phe Gly Glu Ile Glu Gly Ala Val Met
865 870 875 880

Asn Lys Leu Leu Thr Met Gly Ser Phe Lys Arg Ile Thr Leu Tyr Asp
885 890 895

Tyr Gln Ala Met Cys Arg Ala Asn Lys Glu Ser Ser Asp Gly Ala His
900 905 910

Gly Leu Leu Asp Pro Tyr Asn Ala Phe Leu Ser Ala Val Lys Trp Ile
915 920 925

Met Thr Glu Leu Val Leu Phe Leu Val Glu Phe Asn Leu Cys Ser Trp
930 935 940

Trp His Ser Asp Met Thr Ala Lys Ala Gln Lys Leu Lys Gln Thr Leu
945 950 955 960

Glu Pro Cys Asp Thr Glu Tyr Pro Ala Phe Val Ser Glu Arg Thr Ile
965 970 975

Lys Glu Thr Thr Gly Asn Ile Ala Cys Glu Asp Cys Ser Lys Ser Phe
980 985 990

Val Ile Gln Gln Ile Pro Ser Ser Asn Leu Phe Met Val Val Val Asp
995 1000 1005

Ser Ser Cys Leu Cys Glu Ser Val Ala Pro Ile
1010 1015

<210> 11
<211> 1038
<212> PRT
<213> Homo sapiens

<400> 11
Met Ala Gly Pro Gly Ser Pro Arg Arg Ala Ser Arg Gly Ala Ser Ala
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Leu Leu Ala Ala Ala Leu Leu Tyr Ala Ala Leu Gly Asp Val Val Arg
20 25 30

Ser Glu Gln Gln Ile Pro Leu Ser Val Val Lys Leu Trp Ala Ser Ala
35 40 45

Phe Gly Gly Glu Ile Lys Ser Ile Ala Ala Lys Tyr Ser Gly Ser Gln
50 55 60

Leu Leu Gln Lys Lys Tyr Lys Glu Tyr Glu Lys Asp Val Ala Ile Glu
65 70 75 80

Glu Ile Asp Gly Leu Gln Leu Val Lys Lys Leu Ala Lys Asn Met Glu
85 90 95

Glu Met Phe His Lys Lys Ser Glu Ala Val Arg Arg Leu Val Glu Ala
100 105 110

Ala Glu Glu Ala His Leu Lys His Glu Phe Asp Ala Asp Leu Gln Tyr
115 120 125

Glu Tyr Phe Asn Ala Val Leu Ile Asn Glu Arg Asp Lys Asp Gly Asn
130 135 140

Phe Leu Glu Leu Gly Lys Glu Phe Ile Leu Ala Pro Asn Asp His Phe
145 150 155 160

Asn Asn Leu Pro Val Asn Ile Ser Leu Ser Asp Val Gln Val Pro Thr
165 170 175

Asn Met Tyr Asn Lys Asp Pro Ala Ile Val Asn Gly Val Tyr Trp Ser
180 185 190

Glu Ser Leu Asn Lys Val Phe Val Asp Asn Phe Asp Arg Asp Pro Ser
195 200 205

Leu Ile Trp Gln Tyr Phe Gly Ser Ala Lys Gly Phe Phe Arg Gln Tyr
210 215 220

Pro Gly Ile Lys Trp Glu Pro Asp Glu Asn Gly Val Ile Ala Phe Asp
225 230 235 240

Cys Arg Asn Arg Lys Trp Tyr Ile Gln Ala Ala Thr Ser Pro Lys Asp
245 250 255

Val Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu Arg Leu
260 265 270

Thr Ile Ala Lys Gln Thr Val Ser Ser Ile Leu Asp Thr Leu Gly Asp
275 280 285

Asp Asp Phe Phe Asn Ile Ile Ala Tyr Asn Glu Glu Leu His Tyr Val
290 295 300

Glu Pro Cys Leu Asn Gly Thr Leu Val Gln Ala Asp Arg Thr Asn Lys
305 310 315 320

Glu His Phe Arg Glu His Leu Asp Lys Leu Phe Ala Lys Gly Ile Gly
325 330 335

Met Leu Asp Ile Ala Leu Asn Glu Ala Phe Asn Ile Leu Ser Asp Phe
340 345 350

Asn His Thr Gly Gln Gly Ser Ile Cys Ser Gln Ala Ile Met Leu Ile
355 360 365

Thr Asp Gly Ala Val Asp Thr Tyr Asp Thr Ile Phe Ala Lys Tyr Asn

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    370                 375                 380
Trp Pro Asp Arg Lys Val Arg Ile Phe Thr Tyr Leu Ile Gly Arg Glu
385                 390                 395                 400
Ala Ala Phe Ala Asp Asn Leu Lys Trp Met Ala Cys Ala Asn Lys Gly
                405                 410                 415
Phe Phe Thr Gln Ile Ser Thr Leu Ala Asp Val Gln Glu Asn Val Met
            420                 425                 430
Glu Tyr Leu His Val Leu Ser Arg Pro Lys Val Ile Asp Gln Glu His
        435                 440                 445
Asp Val Val Trp Thr Glu Ala Tyr Ile Asp Ser Thr Leu Thr Asp Asp
    450                 455                 460
Gln Gly Pro Val Leu Met Thr Thr Val Ala Met Pro Val Phe Ser Lys
465                 470                 475                 480
Gln Asn Glu Thr Arg Ser Lys Gly Ile Leu Leu Gly Val Val Gly Thr
                485                 490                 495
Asp Val Pro Val Lys Glu Leu Leu Lys Thr Ile Pro Lys Tyr Lys Leu
            500                 505                 510
Gly Ile His Gly Tyr Ala Phe Ala Ile Thr Asn Asn Gly Tyr Ile Leu
        515                 520                 525
Thr His Pro Glu Leu Arg Leu Leu Tyr Glu Glu Gly Lys Lys Arg Arg
    530                 535                 540
Lys Pro Asn Tyr Ser Ser Val Asp Leu Ser Glu Val Glu Trp Glu Asp
545                 550                 555                 560
Arg Asp Asp Val Leu Arg Asn Ala Met Val Asn Arg Lys Thr Gly Lys
                565                 570                 575
Phe Ser Met Glu Val Lys Lys Thr Val Asp Lys Gly Lys Arg Val Leu
            580                 585                 590
Val Met Thr Asn Asp Tyr Tyr Tyr Thr Asp Ile Lys Gly Thr Pro Phe
        595                 600                 605
Ser Leu Gly Val Ala Leu Ser Arg Gly His Gly Lys Tyr Phe Phe Arg
    610                 615                 620
Gly Asn Val Thr Ile Glu Glu Gly Leu His Asp Leu Glu His Pro Asp
625                 630                 635                 640
Val Ser Leu Ala Asp Glu Trp Ser Tyr Cys Asn Thr Asp Leu His Pro
                645                 650                 655
Glu His Arg His Leu Ser Gln Leu Glu Ala Ile Lys Leu Tyr Leu Lys
            660                 665                 670
Gly Lys Glu Pro Leu Leu Gln Cys Asp Lys Glu Leu Ile Gln Glu Val
        675                 680                 685
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Leu Phe Asp Ala Val Val Ser Ala Pro Ile Glu Ala Tyr Trp Thr Ser
690 695 700

Leu Ala Leu Asn Lys Ser Glu Asn Ser Asp Lys Gly Val Glu Val Ala
705 710 715 720

Phe Leu Gly Thr Arg Thr Gly Leu Ser Arg Ile Asn Leu Phe Val Gly
725 730 735

Ala Glu Gln Leu Thr Asn Gln Asp Phe Leu Lys Ala Gly Asp Lys Glu
740 745 750

Asn Ile Phe Asn Ala Asp His Phe Pro Leu Trp Tyr Arg Arg Ala Ala
755 760 765

Glu Gln Ile Pro Gly Ser Phe Val Tyr Ser Ile Pro Phe Ser Thr Gly
770 775 780

Pro Val Asn Lys Ser Asn Val Val Thr Ala Ser Thr Ser Ile Gln Leu
785 790 795 800

Leu Asp Glu Arg Lys Ser Pro Val Val Ala Ala Val Gly Ile Gln Met
805 810 815

Lys Leu Glu Phe Phe Gln Arg Lys Phe Trp Thr Ala Ser Arg Gln Cys
820 825 830

Ala Ser Leu Asp Gly Lys Cys Ser Ile Ser Cys Asp Asp Glu Thr Val
835 840 845

Asn Cys Tyr Leu Ile Asp Asn Asn Gly Phe Ile Leu Val Ser Glu Asp
850 855 860

Tyr Thr Gln Thr Gly Asp Phe Phe Gly Glu Ile Glu Gly Ala Val Met
865 870 875 880

Asn Lys Leu Leu Thr Met Gly Ser Phe Lys Arg Ile Thr Leu Tyr Asp
885 890 895

Tyr Gln Ala Met Cys Arg Ala Asn Lys Glu Ser Ser Asp Gly Ala His
900 905 910

Gly Leu Leu Asp Pro Tyr Asn Ala Phe Leu Ser Ala Val Lys Trp Ile
915 920 925

Met Thr Glu Leu Val Leu Phe Leu Val Glu Phe Asn Leu Cys Ser Trp
930 935 940

Trp His Ser Asp Met Thr Ala Lys Ala Gln Lys Leu Lys Gln Thr Leu
945 950 955 960

Glu Pro Cys Asp Thr Glu Tyr Pro Ala Phe Val Ser Glu Arg Thr Ile
965 970 975

Lys Glu Thr Thr Gly Asn Ile Ala Cys Glu Asp Cys Ser Lys Ser Phe
980 985 990

Val Ile Gln Gln Ile Pro Ser Ser Asn Leu Phe Met Val Val Val Asp
995 1000 1005

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Ser Ser Cys Leu Cys Glu Ser Val Ala Pro Ile Thr Met Ala Pro Ile
   1010                1015                1020

Glu Ile Arg Tyr Asn Glu Ser Leu Lys Cys Glu Arg Leu Lys
1025                1030                1035


<210> 12
<211> 1065
<212> PRT
<213> Homo sapiens

<400> 12
Met Ala Gly Pro Gly Ser Pro Arg Arg Ala Ser Arg Gly Ala Ser Ala
  1               5                  10                  15

Leu Leu Ala Ala Ala Leu Leu Tyr Ala Ala Leu Gly Asp Val Val Arg
             20                  25                  30

Ser Glu Gln Gln Ile Pro Leu Ser Val Val Lys Leu Trp Ala Ser Ala
         35                  40                  45

Phe Gly Gly Glu Ile Lys Ser Ile Ala Ala Lys Tyr Ser Gly Ser Gln
     50                  55                  60

Leu Leu Gln Lys Lys Tyr Lys Glu Tyr Glu Lys Asp Val Ala Ile Glu
 65                  70                  75                  80

Glu Ile Asp Gly Leu Gln Leu Val Lys Lys Leu Ala Lys Asn Met Glu
                 85                  90                  95

Glu Met Phe His Lys Lys Ser Glu Ala Val Arg Arg Leu Val Glu Ala
            100                 105                 110

Ala Glu Glu Ala His Leu Lys His Glu Phe Asp Ala Asp Leu Gln Tyr
        115                 120                 125

Glu Tyr Phe Asn Ala Val Leu Ile Asn Glu Arg Asp Lys Asp Gly Asn
    130                 135                 140

Phe Leu Glu Leu Gly Lys Glu Phe Ile Leu Ala Pro Asn Asp His Phe
145                 150                 155                 160

Asn Asn Leu Pro Val Asn Ile Ser Leu Ser Asp Val Gln Val Pro Thr
                165                 170                 175

Asn Met Tyr Asn Lys Asp Pro Ala Ile Val Asn Gly Val Tyr Trp Ser
            180                 185                 190

Glu Ser Leu Asn Lys Val Phe Val Asp Asn Phe Asp Arg Asp Pro Ser
        195                 200                 205

Leu Ile Trp Gln Tyr Phe Gly Ser Ala Lys Gly Phe Phe Arg Gln Tyr
    210                 215                 220

Pro Gly Ile Lys Trp Glu Pro Asp Glu Asn Gly Val Ile Ala Phe Asp
225                 230                 235                 240
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Cys Arg Asn Arg Lys Trp Tyr Ile Gln Ala Ala Thr Ser Pro Lys Asp
                245                 250                 255

Val Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu Arg Leu
            260                 265                 270

Thr Ile Ala Lys Gln Thr Val Ser Ser Ile Leu Asp Thr Leu Gly Asp
        275                 280                 285

Asp Asp Phe Phe Asn Ile Ile Ala Tyr Asn Glu Glu Leu His Tyr Val
    290                 295                 300

Glu Pro Cys Leu Asn Gly Thr Leu Val Gln Ala Asp Arg Thr Asn Lys
305                 310                 315                 320

Glu His Phe Arg Glu His Leu Asp Lys Leu Phe Ala Lys Gly Ile Gly
                325                 330                 335

Met Leu Asp Ile Ala Leu Asn Glu Ala Phe Asn Ile Leu Ser Asp Phe
            340                 345                 350

Asn His Thr Gly Gln Gly Ser Ile Cys Ser Gln Ala Ile Met Leu Ile
        355                 360                 365

Thr Asp Gly Ala Val Asp Thr Tyr Asp Thr Ile Phe Ala Lys Tyr Asn
    370                 375                 380

Trp Pro Asp Arg Lys Val Arg Ile Phe Thr Tyr Leu Ile Gly Arg Glu
385                 390                 395                 400

Ala Ala Phe Ala Asp Asn Leu Lys Trp Met Ala Cys Ala Asn Lys Gly
                405                 410                 415

Phe Phe Thr Gln Ile Ser Thr Leu Ala Asp Val Gln Glu Asn Val Met
            420                 425                 430

Glu Tyr Leu His Val Leu Ser Arg Pro Lys Val Ile Asp Gln Glu His
        435                 440                 445

Asp Val Val Trp Thr Glu Ala Tyr Ile Asp Ser Thr Leu Thr Asp Asp
    450                 455                 460

Gln Gly Pro Val Leu Met Thr Thr Val Ala Met Pro Val Phe Ser Lys
465                 470                 475                 480

Gln Asn Glu Thr Arg Ser Lys Gly Ile Leu Leu Gly Val Val Gly Thr
                485                 490                 495

Asp Val Pro Val Lys Glu Leu Leu Lys Thr Ile Pro Lys Tyr Lys Leu
            500                 505                 510

Gly Ile His Gly Tyr Ala Phe Ala Ile Thr Asn Asn Gly Tyr Ile Leu
        515                 520                 525

Thr His Pro Glu Leu Arg Leu Leu Tyr Glu Glu Gly Lys Lys Arg Arg
    530                 535                 540

Lys Pro Asn Tyr Ser Ser Val Asp Leu Ser Glu Val Glu Trp Glu Asp
545                 550                 555                 560
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Arg Asp Asp Val Leu Arg Asn Ala Met Val Asn Arg Lys Thr Gly Lys
                565                 570                 575

Phe Ser Met Glu Val Lys Lys Thr Val Asp Lys Gly Lys Arg Val Leu
            580                 585                 590

Val Met Thr Asn Asp Tyr Tyr Tyr Thr Asp Ile Lys Gly Thr Pro Phe
        595                 600                 605

Ser Leu Gly Val Ala Leu Ser Arg Gly His Gly Lys Tyr Phe Phe Arg
    610                 615                 620

Gly Asn Val Thr Ile Glu Glu Gly Leu His Asp Leu Glu His Pro Asp
625                 630                 635                 640

Val Ser Leu Ala Asp Glu Trp Ser Tyr Cys Asn Thr Asp Leu His Pro
                645                 650                 655

Glu His Arg His Leu Ser Gln Leu Glu Ala Ile Lys Leu Tyr Leu Lys
            660                 665                 670

Gly Lys Glu Pro Leu Leu Gln Cys Asp Lys Glu Leu Ile Gln Glu Val
        675                 680                 685

Leu Phe Asp Ala Val Val Ser Ala Pro Ile Glu Ala Tyr Trp Thr Ser
    690                 695                 700

Leu Ala Leu Asn Lys Ser Glu Asn Ser Asp Lys Gly Val Glu Val Ala
705                 710                 715                 720

Phe Leu Gly Thr Arg Thr Gly Leu Ser Arg Ile Asn Leu Phe Val Gly
                725                 730                 735

Ala Glu Gln Leu Thr Asn Gln Asp Phe Leu Lys Ala Gly Asp Lys Glu
            740                 745                 750

Asn Ile Phe Asn Ala Asp His Phe Pro Leu Trp Tyr Arg Arg Ala Ala
        755                 760                 765

Glu Gln Ile Pro Gly Ser Phe Val Tyr Ser Ile Pro Phe Ser Thr Gly
    770                 775                 780

Pro Val Asn Lys Ser Asn Val Val Thr Ala Ser Thr Ser Ile Gln Leu
785                 790                 795                 800

Leu Asp Glu Arg Lys Ser Pro Val Val Ala Ala Val Gly Ile Gln Met
                805                 810                 815

Lys Leu Glu Phe Phe Gln Arg Lys Phe Trp Thr Ala Ser Arg Gln Cys
            820                 825                 830

Ala Ser Leu Asp Gly Lys Cys Ser Ile Ser Cys Asp Asp Glu Thr Val
        835                 840                 845

Asn Cys Tyr Leu Ile Asp Asn Asn Gly Phe Ile Leu Val Ser Glu Asp
    850                 855                 860

Tyr Thr Gln Thr Gly Asp Phe Phe Gly Glu Ile Glu Gly Ala Val Met
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865 870 875 880

Asn Lys Leu Leu Thr Met Gly Ser Phe Lys Arg Ile Thr Leu Tyr Asp
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Tyr Gln Ala Met Cys Arg Ala Asn Lys Glu Ser Ser Asp Gly Ala His
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Gly Leu Leu Asp Pro Tyr Asn Ala Phe Leu Ser Ala Val Lys Trp Ile
915 920 925

Met Thr Glu Leu Val Leu Phe Leu Val Glu Phe Asn Leu Cys Ser Trp
930 935 940

Trp His Ser Asp Met Thr Ala Lys Ala Gln Lys Leu Lys Gln Thr Leu
945 950 955 960

Glu Pro Cys Asp Thr Glu Tyr Pro Ala Phe Val Ser Glu Arg Thr Ile
965 970 975

Lys Glu Thr Thr Gly Asn Ile Ala Cys Glu Asp Cys Ser Lys Ser Phe
980 985 990

Val Ile Gln Gln Ile Pro Ser Ser Asn Leu Phe Met Val Val Val Asp
995 1000 1005

Ser Ser Cys Leu Cys Glu Ser Val Ala Pro Ile Thr Met Ala Pro Ile
1010 1015 1020

Glu Ile Arg Tyr Asn Glu Ser Leu Lys Cys Glu Arg Leu Lys Ala Gln
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<212> DNA
<213> Homo sapiens

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<212> PRT
<213> Homo sapiens

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Asp Arg Phe Pro Leu Trp Tyr Arg Gln Ala Ser Glu His Pro Ala Gly
35 40 45

Ser Phe Val Phe Asn Leu Arg Trp Ala Glu Gly Pro Glu Ser Ala Gly
50 55 60

Glu Pro Met Val Val Thr Ala Ser Thr Ala Val Ala Val Thr Val Asp
65 70 75 80

Lys Arg Thr Ala Ile Ala Ala Ala Ala Gly Val Gln Met Lys Leu Glu
85 90 95

Phe Leu Gln Arg Lys Phe Trp Ala Ala Thr Arg Gln Cys Ser Thr Val
100 105 110

Asp Gly Pro Cys Thr Gln Ser Cys Glu Asp Ser Asp Leu Asp Cys Phe
115 120 125

Val Ile Asp Asn Asn Gly Phe Ile Leu Ile Ser Lys Arg Ser Arg Glu
130 135 140

Thr Gly Arg Phe Leu Gly Glu Val Asp Gly Ala Val Leu Thr Gln Leu
145 150 155 160

Leu Ser Met Gly Val Phe Ser Gln Val Thr Met Tyr Asp Tyr Gln Ala
165 170 175

Met Cys Lys Pro Ser Ser His His His Ser Ala Ala Gln Pro Leu Val
180 185 190

Ser Pro Ile Ser Ala Phe Leu Thr Ala Thr Arg Trp Leu Leu Gln Glu
195 200 205

Leu Val Leu Phe Leu Leu Glu Trp Ser Val Trp Gly Ser Trp Tyr Asp
210 215 220

Arg Gly Ala Glu Ala Lys Ser Val Phe His His Ser His Lys His Lys
225 230 235 240

Lys Gln Asp Pro Leu Gln Pro Cys Asp Thr Glu Tyr Pro Val Phe Val
245 250 255

Tyr Gln Pro Ala Ile Arg Glu Ala Asn Gly Ile Val Glu Cys Gly Pro
260 265 270

Cys Gln Lys Val Phe Val Val Gln Gln Ile Pro Asn Ser Asn Leu Leu
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Leu Leu Val Thr Asp Pro Thr Cys Asp Cys Ser Ile Phe Pro Pro Val
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<210> 17
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Asp Arg Phe Pro Leu Trp Tyr Arg Gln Ala Ser Glu His Pro Ala Gly
35 40 45

Ser Phe Val Phe Asn Leu Arg Trp Ala Glu Gly Pro Glu Ser Ala Gly
50 55 60

Glu Pro Met Val Val Thr Ala Ser Thr Ala Val Ala Val Thr Val Asp
65 70 75 80

Lys Arg Thr Ala Ile Ala Ala Ala Ala Gly Val Gln Met Lys Leu Glu
85 90 95

Phe Leu Gln Arg Lys Phe Trp Ala Ala Thr Arg Gln Cys Ser Thr Val
100 105 110

Asp Gly Pro Cys Thr Gln Ser Cys Glu Asp Ser Asp Leu Asp Cys Phe
115 120 125

Val Ile Asp Asn Asn Gly Phe Ile Leu Ile Ser Lys Arg Ser Arg Glu
130 135 140

Thr Gly Arg Phe Leu Gly Glu Val Asp Gly Ala Val Leu Thr Gln Leu
145 150 155 160

Leu Ser Met Gly Val Phe Ser Gln Val Thr Met Tyr Asp Tyr Gln Ala
165 170 175

Met Cys Lys Pro Ser Ser His His His Ser Ala Ala Gln Pro Leu Val
180 185 190

Ser Pro Ile Ser Ala Phe Leu Thr Ala Thr Arg Trp Leu Leu Gln Glu
195 200 205

Leu Val Leu Phe Leu Leu Glu Trp Ser Val Trp Gly Ser Trp Tyr Asp
210 215 220

Arg Gly Ala Glu Ala Lys Ser Val Phe His His Ser His Lys His Lys
225 230 235 240

Lys Gln Asp Pro Leu Gln Pro Cys Asp Thr Glu Tyr Pro Val Phe Val
245 250 255

Tyr Gln Pro Ala Ile Arg Glu Ala Asn Gly Ile Val Glu Cys Gly Pro

260 265 270

Cys Gln Lys Val Phe Val Val Gln Gln Ile Pro Asn Ser Asn Leu Leu
275 280 285

Leu Leu Val Thr Asp Pro Thr Cys Asp Cys Ser Ile Phe Pro Pro Val
290 295 300

Leu Gln Glu Ala Thr Glu Val Lys Tyr Asn Ala Ser Val Lys Cys Asp
305 310 315 320

Arg Met Arg

<210> 18
<211> 350
<212> PRT
<213> Homo sapiens

<400> 18
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Asp Arg Lys Phe Leu Thr Pro Glu Asp Glu Ala Ser Val Phe Thr Leu
20 25 30

Asp Arg Phe Pro Leu Trp Tyr Arg Gln Ala Ser Glu His Pro Ala Gly
35 40 45

Ser Phe Val Phe Asn Leu Arg Trp Ala Glu Gly Pro Glu Ser Ala Gly
50 55 60

Glu Pro Met Val Val Thr Ala Ser Thr Ala Val Ala Val Thr Val Asp
65 70 75 80

Lys Arg Thr Ala Ile Ala Ala Ala Ala Gly Val Gln Met Lys Leu Glu
85 90 95

Phe Leu Gln Arg Lys Phe Trp Ala Ala Thr Arg Gln Cys Ser Thr Val
100 105 110

Asp Gly Pro Cys Thr Gln Ser Cys Glu Asp Ser Asp Leu Asp Cys Phe
115 120 125

Val Ile Asp Asn Asn Gly Phe Ile Leu Ile Ser Lys Arg Ser Arg Glu
130 135 140

Thr Gly Arg Phe Leu Gly Glu Val Asp Gly Ala Val Leu Thr Gln Leu
145 150 155 160

Leu Ser Met Gly Val Phe Ser Gln Val Thr Met Tyr Asp Tyr Gln Ala
165 170 175

Met Cys Lys Pro Ser Ser His His His Ser Ala Ala Gln Pro Leu Val
180 185 190

Ser Pro Ile Ser Ala Phe Leu Thr Ala Thr Arg Trp Leu Leu Gln Glu
195 200 205

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Leu Val Leu Phe Leu Leu Glu Trp Ser Val Trp Gly Ser Trp Tyr Asp
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Arg Gly Ala Glu Ala Lys Ser Val Phe His His Ser His Lys His Lys
225                 230                 235                 240

Lys Gln Asp Pro Leu Gln Pro Cys Asp Thr Glu Tyr Pro Val Phe Val
                245                 250                 255

Tyr Gln Pro Ala Ile Arg Glu Ala Asn Gly Ile Val Glu Cys Gly Pro
            260                 265                 270

Cys Gln Lys Val Phe Val Val Gln Gln Ile Pro Asn Ser Asn Leu Leu
        275                 280                 285

Leu Leu Val Thr Asp Pro Thr Cys Asp Cys Ser Ile Phe Pro Pro Val
    290                 295                 300

Leu Gln Glu Ala Thr Glu Val Lys Tyr Asn Ala Ser Val Lys Cys Asp
305                 310                 315                 320

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<212> DNA
<213> Homo sapiens

<400> 19

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<212> PRT
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Thr Arg Arg Pro Thr Ser Gly Pro Pro Arg Pro Leu Trp Leu Leu Leu
35 40 45

Pro Leu Leu Pro Leu Leu Ala Ala Pro Gly Ala Ser Ala Tyr Ser Phe
50 55 60

Pro Gln Gln His Thr Met Gln His Trp Ala Arg Arg Leu Glu Gln Glu
65 70 75 80

Val Asp Gly Val Met Arg Ile Phe Gly Gly Val Gln Gln Leu Arg Glu
85 90 95

Ile Tyr Lys Asp Asn Arg Asn Leu Phe Glu Val Gln Glu Asn Glu Pro
100 105 110

Gln Lys Leu Val Glu Lys Val Ala Gly Asp Ile Glu Ser Leu Leu Asp
115 120 125

Arg Lys Val Gln Ala Leu Lys Arg Leu Ala Asp Ala Ala Glu Asn Phe
130 135 140

Gln Lys Ala His Arg Trp Gln Asp Asn Ile Lys Glu Glu Asp Ile Val
145 150 155 160

Tyr Tyr Asp Ala Lys Ala Asp Ala Glu Leu Asp Asp Pro Glu Ser Glu
165 170 175

Asp Val Glu Arg Gly Ser Lys Ala Ser Thr Leu Arg Leu Asp Phe Ile
180 185 190

Glu Asp Pro Asn Phe Lys Asn Lys Val Asn Tyr Ser Tyr Ala Ala Val
195 200 205

Gln Ile Pro Thr Asp Ile Tyr Lys Gly Ser Thr Val Ile Leu Asn Glu
210 215 220

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Gln Asp Pro Thr Leu Leu Trp Gln Val Phe Gly Ser Ala Thr Gly Val
                245                 250                 255

Thr Arg Tyr Tyr Pro Ala Thr Pro Trp Arg Ala Pro Lys Lys Ile Asp
            260                 265                 270

Leu Tyr Asp Val Arg Arg Arg Pro Trp Tyr Ile Gln Gly Ala Ser Ser
        275                 280                 285

Pro Lys Asp Met Val Ile Ile Val Asp Val Ser Gly Ser Val Ser Gly
    290                 295                 300

Leu Thr Leu Lys Leu Met Lys Thr Ser Val Cys Glu Met Leu Asp Thr
305                 310                 315                 320

Leu Ser Asp Asp Asp Tyr Val Asn Val Ala Ser Phe Asn Glu Lys Ala
                325                 330                 335

Gln Pro Val Ser Cys Phe Thr His Leu Val Gln Ala Asn Val Arg Asn
            340                 345                 350

Lys Lys Val Phe Lys Glu Ala Val Gln Gly Met Val Ala Lys Gly Thr
        355                 360                 365

Thr Gly Tyr Lys Ala Gly Phe Glu Tyr Ala Phe Asp Gln Leu Gln Asn
    370                 375                 380

Ser Asn Ile Thr Arg Ala Asn Cys Asn Lys Met Ile Met Met Phe Thr
385                 390                 395                 400

Asp Gly Gly Glu Asp Arg Val Gln Asp Val Phe Glu Lys Tyr Asn Trp
                405                 410                 415

Pro Asn Arg Thr Val Arg Val Phe Thr Phe Ser Val Gly Gln His Asn
            420                 425                 430

Tyr Asp Val Thr Pro Leu Gln Trp Met Ala Cys Ala Asn Lys Gly Tyr
        435                 440                 445

Tyr Phe Glu Ile Pro Ser Ile Gly Ala Ile Arg Ile Asn Thr Gln Glu
    450                 455                 460

Tyr Leu Asp Val Leu Gly Arg Pro Met Val Leu Ala Gly Lys Glu Ala
465                 470                 475                 480

Lys Gln Val Gln Trp Thr Asn Val Tyr Glu Asp Ala Leu Gly Leu Gly
                485                 490                 495

Leu Val Val Thr Gly Thr Leu Pro Val Phe Asn Leu Thr Gln Asp Gly
            500                 505                 510

Pro Gly Glu Lys Lys Asn Gln Leu Ile Leu Gly Val Met Gly Ile Asp
        515                 520                 525

Val Ala Leu Asn Asp Ile Lys Arg Leu Thr Pro Asn Tyr Thr Leu Gly
    530                 535                 540
```

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Ala Asn Gly Tyr Val Phe Ala Ile Asp Leu Asn Gly Tyr Val Leu Leu
545                 550                 555                 560

His Pro Asn Leu Lys Pro Gln Thr Thr Asn Phe Arg Glu Pro Val Thr
                565                 570                 575

Leu Asp Phe Leu Asp Ala Glu Leu Glu Asp Glu Asn Lys Glu Glu Ile
            580                 585                 590

Arg Arg Ser Met Ile Asp Gly Asn Lys Gly His Lys Gln Ile Arg Thr
        595                 600                 605

Leu Val Lys Ser Leu Asp Glu Arg Tyr Ile Asp Glu Val Thr Arg Asn
    610                 615                 620

Tyr Thr Trp Val Pro Ile Arg Ser Thr Asn Tyr Ser Leu Gly Leu Val
625                 630                 635                 640

Leu Pro Pro Tyr Ser Thr Phe Tyr Leu Gln Ala Asn Leu Ser Asp Gln
                645                 650                 655

Ile Leu Gln Val Lys Tyr Phe Glu Phe Leu Leu Pro Ser Ser Phe Glu
            660                 665                 670

Ser Glu Gly His Val Phe Ile Ala Pro Arg Glu Tyr Cys Lys Asp Leu
        675                 680                 685

Asn Ala Ser Asp Asn Asn Thr Glu Phe Leu Lys Asn Phe Ile Glu Leu
    690                 695                 700

Met Glu Lys Val Thr Pro Asp Ser Lys Gln Cys Asn Asn Phe Leu Leu
705                 710                 715                 720

His Asn Leu Ile Leu Asp Thr Gly Ile Thr Gln Gln Leu Val Glu Arg
                725                 730                 735

Val Trp Arg Asp Gln Asp Leu Asn Thr Tyr Ser Leu Leu Ala Val Phe
            740                 745                 750

Ala Ala Thr Asp Gly Gly Ile Thr Arg Val Phe Pro Asn Lys Ala Ala
        755                 760                 765

Glu Asp Trp Thr Glu Asn Pro Glu Pro Phe Asn Ala Ser Phe Tyr Arg
    770                 775                 780

Arg Ser Leu Asp Asn His Gly Tyr Val Phe Lys Pro Pro His Gln Asp
785                 790                 795                 800

Ala Leu Leu Arg Pro Leu Glu Leu Glu Asn Asp Thr Val Gly Ile Leu
                805                 810                 815

Val Ser Thr Ala Val Glu Leu Ser Leu Gly Arg Arg Thr Leu Arg Pro
            820                 825                 830

Ala Val Val Gly Val Lys Leu Asp Leu Glu Ala Trp Ala Glu Lys Phe
        835                 840                 845

Lys Val Leu Ala Ser Asn Arg Thr His Gln Asp Gln Pro Gln Lys Cys
```

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     850                 855                 860

Gly Pro Asn Ser His Cys Glu Met Asp Cys Glu Val Asn Asn Glu Asp
865                 870                 875                 880

Leu Leu Cys Val Leu Ile Asp Asp Gly Gly Phe Leu Val Leu Ser Asn
                885                 890                 895

Gln Asn His Gln Trp Asp Gln Val Gly Arg Phe Phe Ser Glu Val Asp
            900                 905                 910

Ala Asn Leu Met Leu Ala Leu Tyr Asn Asn Ser Phe Tyr Thr Arg Lys
        915                 920                 925

Glu Ser Tyr Asp Tyr Gln Ala Ala Cys Ala Pro Gln Pro Pro Gly Asn
    930                 935                 940

Leu Gly Ala Ala Pro Arg Gly Val Phe Val Pro Thr Val Ala Asp Phe
945                 950                 955                 960

Leu Asn Leu Ala Trp Trp Thr Ser Ala Ala Ala Trp Ser Leu Phe Gln
                965                 970                 975

Gln Leu Leu Tyr Gly Leu Ile Tyr His Ser Trp Phe Gln Ala Asp Pro
            980                 985                 990

Ala Glu Ala Glu Gly Ser Pro Glu Thr Arg Glu Ser Ser Cys Val Met
        995                1000                1005

Lys Gln Thr Gln Tyr Tyr Phe Gly Ser Val Asn Ala Ser Tyr Asn Ala
   1010                1015                1020

Ile Ile Asp Cys Gly Asn Cys Ser Arg Leu Phe His Ala Gln Arg Leu
1025                1030                1035                1040

Thr Asn Thr Asn Leu Leu Phe Val Val Ala Glu Lys Pro Leu Cys Ser
                1045                1050                1055

Gln Cys Glu Ala Gly Arg Leu Leu Gln Lys Glu Thr His Cys Pro Ala
            1060                1065                1070

Asp Gly Pro Glu Gln Cys Glu Leu Val Gln Arg Pro Arg Tyr Arg Arg
        1075                1080                1085

Gly Pro His Ile Cys Phe Asp Tyr Asn Ala Thr Glu Asp Thr Ser Asp
   1090                1095                1100

Cys Gly Arg Gly Ala Ser Phe Pro Pro Ser Leu Gly Val Leu Val Ser
1105                1110                1115                1120

Leu Gln Leu Leu Leu Leu Leu Gly Leu Pro Pro Arg Pro Gln Pro Gln
                1125                1130                1135

Val Leu Val His Ala Ser Arg Arg Leu
            1140                1145
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<211> 3770

<212> DNA
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ctgtgctgat aaatgaaagg gacaaagacg ggaatttttt ggagctggga aaggaattca 600
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<211> 1085
<212> PRT
<213> Homo sapiens

<400> 22
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Leu Leu Ala Ala Ala Leu Leu Tyr Ala Ala Leu Gly Asp Val Val Arg
20 25 30

Ser Glu Gln Gln Ile Pro Leu Ser Val Val Lys Leu Trp Ala Ser Ala
35 40 45

Phe Gly Gly Glu Ile Lys Ser Ile Ala Ala Lys Tyr Ser Gly Ser Gln
50 55 60

Leu Leu Gln Lys Lys Tyr Lys Glu Tyr Glu Lys Asp Val Ala Ile Glu
65 70 75 80

Glu Ile Asp Gly Leu Gln Leu Val Lys Lys Leu Ala Lys Asn Met Glu
85 90 95

Glu Met Phe His Lys Lys Ser Glu Ala Val Arg Arg Leu Val Glu Ala
100 105 110

Ala Glu Glu Ala His Leu Lys His Glu Phe Asp Ala Asp Leu Gln Tyr
115 120 125

Glu Tyr Phe Asn Ala Val Leu Ile Asn Glu Arg Asp Lys Asp Gly Asn
130 135 140

Phe Leu Glu Leu Gly Lys Glu Phe Ile Leu Ala Pro Asn Asp His Phe
145 150 155 160

Asn Asn Leu Pro Val Asn Ile Ser Leu Ser Asp Val Gln Val Pro Thr
165 170 175

Asn Met Tyr Asn Lys Asp Pro Ala Ile Val Asn Gly Val Tyr Trp Ser
180 185 190

Glu Ser Leu Asn Lys Val Phe Val Asp Asn Phe Asp Arg Asp Pro Ser
195 200 205

Leu Ile Trp Gln Tyr Phe Gly Ser Ala Lys Gly Phe Phe Arg Gln Tyr
210 215 220

Pro Gly Ile Lys Trp Glu Pro Asp Glu Asn Gly Val Ile Ala Phe Asp

```
225                 230                 235                 240

Cys Arg Asn Arg Lys Trp Tyr Ile Gln Ala Ala Thr Ser Pro Lys Asp
                245                 250                 255

Val Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu Arg Leu
            260                 265                 270

Thr Ile Ala Lys Gln Thr Val Ser Ser Ile Leu Asp Thr Leu Gly Asp
        275                 280                 285

Asp Asp Phe Phe Asn Ile Ile Ala Tyr Asn Glu Glu Leu His Tyr Val
    290                 295                 300

Glu Pro Cys Leu Asn Gly Thr Leu Val Gln Ala Asp Arg Thr Asn Lys
305                 310                 315                 320

Glu His Phe Arg Glu His Leu Asp Lys Leu Phe Ala Lys Gly Ile Gly
                325                 330                 335

Met Leu Asp Ile Ala Leu Asn Glu Ala Phe Asn Ile Leu Ser Asp Phe
            340                 345                 350

Asn His Thr Gly Gln Gly Ser Ile Cys Ser Gln Ala Ile Met Leu Ile
        355                 360                 365

Thr Asp Gly Ala Val Asp Thr Tyr Asp Thr Ile Phe Ala Lys Tyr Asn
    370                 375                 380

Trp Pro Asp Arg Lys Val Arg Ile Phe Thr Tyr Leu Ile Gly Arg Glu
385                 390                 395                 400

Ala Ala Phe Ala Asp Asn Leu Lys Trp Met Ala Cys Ala Asn Lys Gly
                405                 410                 415

Phe Phe Thr Gln Ile Ser Thr Leu Ala Asp Val Gln Glu Asn Val Met
            420                 425                 430

Glu Tyr Leu His Val Leu Ser Arg Pro Lys Val Ile Asp Gln Glu His
        435                 440                 445

Asp Val Val Trp Thr Glu Ala Tyr Ile Asp Ser Thr Leu Thr Asp Asp
    450                 455                 460

Gln Gly Pro Val Leu Met Thr Thr Val Ala Met Pro Val Phe Ser Lys
465                 470                 475                 480

Gln Asn Glu Thr Arg Ser Lys Gly Ile Leu Leu Gly Val Val Gly Thr
                485                 490                 495

Asp Val Pro Val Lys Glu Leu Leu Lys Thr Ile Pro Lys Tyr Lys Leu
            500                 505                 510

Gly Ile His Gly Tyr Ala Phe Ala Ile Thr Asn Asn Gly Tyr Ile Leu
        515                 520                 525

Thr His Pro Glu Leu Arg Leu Leu Tyr Glu Glu Gly Lys Lys Arg Arg
    530                 535                 540
```

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Lys Pro Asn Tyr Ser Ser Val Asp Leu Ser Glu Val Glu Trp Glu Asp
545                 550                 555                 560

Arg Asp Asp Val Leu Arg Asn Ala Met Val Asn Arg Lys Thr Gly Lys
                565                 570                 575

Phe Ser Met Glu Val Lys Lys Thr Val Asp Lys Gly Lys Arg Val Leu
            580                 585                 590

Val Met Thr Asn Asp Tyr Tyr Tyr Thr Asp Ile Lys Gly Thr Pro Phe
        595                 600                 605

Ser Leu Gly Val Ala Leu Ser Arg Gly His Gly Lys Tyr Phe Phe Arg
    610                 615                 620

Gly Asn Val Thr Ile Glu Glu Gly Leu His Asp Leu Glu His Pro Asp
625                 630                 635                 640

Val Ser Leu Ala Asp Glu Trp Ser Tyr Cys Asn Thr Asp Leu His Pro
                645                 650                 655

Glu His Arg His Leu Ser Gln Leu Glu Ala Ile Lys Leu Tyr Leu Lys
            660                 665                 670

Gly Lys Glu Pro Leu Leu Gln Cys Asp Lys Glu Leu Ile Gln Glu Val
        675                 680                 685

Leu Phe Asp Ala Val Val Ser Ala Pro Ile Glu Ala Tyr Trp Thr Ser
    690                 695                 700

Leu Ala Leu Asn Lys Ser Glu Asn Ser Asp Lys Gly Val Glu Val Ala
705                 710                 715                 720

Phe Leu Gly Thr Arg Thr Gly Leu Ser Arg Ile Asn Leu Phe Val Gly
                725                 730                 735

Ala Glu Gln Leu Thr Asn Gln Asp Phe Leu Lys Ala Gly Asp Lys Glu
            740                 745                 750

Asn Ile Phe Asn Ala Asp His Phe Pro Leu Trp Tyr Arg Arg Ala Ala
        755                 760                 765

Glu Gln Ile Pro Gly Ser Phe Val Tyr Ser Ile Pro Phe Ser Thr Gly
    770                 775                 780

Pro Val Asn Lys Ser Asn Val Val Thr Ala Ser Thr Ser Ile Gln Leu
785                 790                 795                 800

Leu Asp Glu Arg Lys Ser Pro Val Val Ala Ala Val Gly Ile Gln Met
                805                 810                 815

Lys Leu Glu Phe Phe Gln Arg Lys Phe Trp Thr Ala Ser Arg Gln Cys
            820                 825                 830

Ala Ser Leu Asp Gly Lys Cys Ser Ile Ser Cys Asp Asp Glu Thr Val
        835                 840                 845

Asn Cys Tyr Leu Ile Asp Asn Asn Gly Phe Ile Leu Val Ser Glu Asp
    850                 855                 860
```

```
Tyr Thr Gln Thr Gly Asp Phe Phe Gly Glu Ile Glu Gly Ala Val Met
865                 870                 875                 880

Asn Lys Leu Leu Thr Met Gly Ser Phe Lys Arg Ile Thr Leu Tyr Asp
                885                 890                 895

Tyr Gln Ala Met Cys Arg Ala Asn Lys Glu Ser Ser Asp Gly Ala His
            900                 905                 910

Gly Leu Leu Asp Pro Tyr Asn Ala Phe Leu Ser Ala Val Lys Trp Ile
        915                 920                 925

Met Thr Glu Leu Val Leu Phe Leu Val Glu Phe Asn Leu Cys Ser Trp
    930                 935                 940

Trp His Ser Asp Met Thr Ala Lys Ala Gln Lys Leu Lys Gln Thr Leu
945                 950                 955                 960

Glu Pro Cys Asp Thr Glu Tyr Pro Ala Phe Val Ser Glu Arg Thr Ile
                965                 970                 975

Lys Glu Thr Thr Gly Asn Ile Ala Cys Glu Asp Cys Ser Lys Ser Phe
            980                 985                 990

Val Ile Gln Gln Ile Pro Ser Ser Asn Leu Phe Met Val Val Val Asp
        995                1000                1005

Ser Ser Cys Leu Cys Glu Ser Val Ala Pro Ile Thr Met Ala Pro Ile
   1010                1015                1020

Glu Ile Arg Tyr Asn Glu Ser Leu Lys Cys Glu Arg Leu Lys Ala Gln
1025                1030                1035                1040

Lys Ile Arg Arg Arg Pro Glu Ser Cys His Gly Phe His Pro Glu Glu
                1045                1050                1055

Asn Ala Arg Glu Cys Gly Gly Ala Pro Ser Leu Gln Ala Gln Thr Val
            1060                1065                1070

Leu Leu Leu Leu Pro Leu Leu Leu Met Leu Phe Ser Arg
        1075                1080                1085


<210> 23
<211> 1115
<212> PRT
<213> Homo sapiens

<400> 23
Met Ala Val Pro Ala Arg Thr Cys Gly Ala Ser Arg Pro Gly Pro Ala
  1               5                  10                  15

Arg Thr Ala Arg Pro Trp Pro Gly Cys Gly Pro His Pro Gly Pro Gly
            20                  25                  30

Thr Arg Arg Pro Thr Ser Gly Pro Pro Arg Pro Leu Trp Leu Leu Leu
        35                  40                  45
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```
Pro Leu Leu Pro Leu Leu Ala Ala Pro Gly Ala Ser Ala Tyr Ser Phe
     50                  55                  60

Pro Gln Gln His Thr Met Gln His Trp Ala Arg Arg Leu Glu Gln Glu
 65                  70                  75                  80

Val Asp Gly Val Met Arg Ile Phe Gly Gly Val Gln Gln Leu Arg Glu
                 85                  90                  95

Ile Tyr Lys Asp Asn Arg Asn Leu Phe Glu Val Gln Glu Asn Glu Pro
            100                 105                 110

Gln Lys Leu Val Glu Lys Val Ala Gly Asp Ile Glu Ser Leu Leu Asp
        115                 120                 125

Arg Lys Val Gln Ala Leu Lys Arg Leu Ala Asp Ala Ala Glu Asn Phe
    130                 135                 140

Gln Lys Ala His Arg Trp Gln Asp Asn Ile Lys Glu Glu Asp Ile Val
145                 150                 155                 160

Tyr Tyr Asp Ala Lys Ala Asp Ala Glu Leu Asp Asp Pro Glu Ser Glu
                165                 170                 175

Asp Val Glu Arg Gly Ser Lys Ala Ser Thr Leu Arg Leu Asp Phe Ile
            180                 185                 190

Glu Asp Pro Asn Phe Lys Asn Lys Val Asn Tyr Ser Tyr Ala Ala Val
        195                 200                 205

Gln Ile Pro Thr Asp Ile Tyr Lys Gly Ser Thr Val Ile Leu Asn Glu
    210                 215                 220

Leu Asn Trp Thr Glu Ala Leu Glu Asn Val Phe Met Glu Asn Arg Arg
225                 230                 235                 240

Gln Asp Pro Thr Leu Leu Trp Gln Val Phe Gly Ser Ala Thr Gly Val
                245                 250                 255

Thr Arg Tyr Tyr Pro Ala Thr Pro Trp Arg Ala Pro Lys Lys Ile Asp
            260                 265                 270

Leu Tyr Asp Val Arg Arg Arg Pro Trp Tyr Ile Gln Gly Ala Ser Ser
        275                 280                 285

Pro Lys Asp Met Val Ile Ile Val Asp Val Ser Gly Ser Val Ser Gly
    290                 295                 300

Leu Thr Leu Lys Leu Met Lys Thr Ser Val Cys Glu Met Leu Asp Thr
305                 310                 315                 320

Leu Ser Asp Asp Asp Tyr Val Asn Val Ala Ser Phe Asn Glu Lys Ala
                325                 330                 335

Gln Pro Val Ser Cys Phe Thr His Leu Val Gln Ala Asn Val Arg Asn
            340                 345                 350

Lys Lys Val Phe Lys Glu Ala Val Gln Gly Met Val Ala Lys Gly Thr
        355                 360                 365
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Thr Gly Tyr Lys Ala Gly Phe Glu Tyr Ala Phe Asp Gln Leu Gln Asn
    370                 375                 380

Ser Asn Ile Thr Arg Ala Asn Cys Asn Lys Met Ile Met Met Phe Thr
385                 390                 395                 400

Asp Gly Gly Glu Asp Arg Val Gln Asp Val Phe Glu Lys Tyr Asn Trp
                405                 410                 415

Pro Asn Arg Thr Val Arg Val Phe Thr Phe Ser Val Gly Gln His Asn
            420                 425                 430

Tyr Asp Val Thr Pro Leu Gln Trp Met Ala Cys Ala Asn Lys Gly Tyr
        435                 440                 445

Tyr Phe Glu Ile Pro Ser Ile Gly Ala Ile Arg Ile Asn Thr Gln Glu
    450                 455                 460

Tyr Leu Asp Val Leu Gly Arg Pro Met Val Leu Ala Gly Lys Glu Ala
465                 470                 475                 480

Lys Gln Val Gln Trp Thr Asn Val Tyr Glu Asp Ala Leu Gly Leu Gly
                485                 490                 495

Leu Val Val Thr Gly Thr Leu Pro Val Phe Asn Leu Thr Gln Asp Gly
            500                 505                 510

Pro Gly Glu Lys Lys Asn Gln Leu Ile Leu Gly Val Met Gly Ile Asp
        515                 520                 525

Val Ala Leu Asn Asp Ile Lys Arg Leu Thr Pro Asn Tyr Thr Leu Gly
    530                 535                 540

Ala Asn Gly Tyr Val Phe Ala Ile Asp Leu Asn Gly Tyr Val Leu Leu
545                 550                 555                 560

His Pro Asn Leu Lys Pro Gln Thr Thr Asn Phe Arg Glu Pro Val Thr
                565                 570                 575

Leu Asp Phe Leu Asp Ala Glu Leu Glu Asp Glu Asn Lys Glu Glu Ile
            580                 585                 590

Arg Arg Ser Met Ile Asp Gly Asn Lys Gly His Lys Gln Ile Arg Thr
        595                 600                 605

Leu Val Lys Ser Leu Asp Glu Arg Tyr Ile Asp Glu Val Thr Arg Asn
    610                 615                 620

Tyr Thr Trp Val Pro Ile Arg Ser Thr Asn Tyr Ser Leu Gly Leu Val
625                 630                 635                 640

Leu Pro Pro Tyr Ser Thr Phe Tyr Leu Gln Ala Asn Leu Ser Asp Gln
                645                 650                 655

Ile Leu Gln Val Lys Tyr Phe Glu Phe Leu Leu Pro Ser Ser Phe Glu
            660                 665                 670

Ser Glu Gly His Val Phe Ile Ala Pro Arg Glu Tyr Cys Lys Asp Leu
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675 680 685

Asn Ala Ser Asp Asn Asn Thr Glu Phe Leu Lys Asn Phe Ile Glu Leu
690 695 700

Met Glu Lys Val Thr Pro Asp Ser Lys Gln Cys Asn Asn Phe Leu Leu
705 710 715 720

His Asn Leu Ile Leu Asp Thr Gly Ile Thr Gln Gln Leu Val Glu Arg
725 730 735

Val Trp Arg Asp Gln Asp Leu Asn Thr Tyr Ser Leu Leu Ala Val Phe
740 745 750

Ala Ala Thr Asp Gly Gly Ile Thr Arg Val Phe Pro Asn Lys Ala Ala
755 760 765

Glu Asp Trp Thr Glu Asn Pro Glu Pro Phe Asn Ala Ser Phe Tyr Arg
770 775 780

Arg Ser Leu Asp Asn His Gly Tyr Val Phe Lys Pro Pro His Gln Asp
785 790 795 800

Ala Leu Leu Arg Pro Leu Glu Leu Glu Asn Asp Thr Val Gly Ile Leu
805 810 815

Val Ser Thr Ala Val Glu Leu Ser Leu Gly Arg Arg Thr Leu Arg Pro
820 825 830

Ala Val Val Gly Val Lys Leu Asp Leu Glu Ala Trp Ala Glu Lys Phe
835 840 845

Lys Val Leu Ala Ser Asn Arg Thr His Gln Asp Gln Pro Gln Lys Cys
850 855 860

Gly Pro Asn Ser His Cys Glu Met Asp Cys Glu Val Asn Asn Glu Asp
865 870 875 880

Leu Leu Cys Val Leu Ile Asp Asp Gly Gly Phe Leu Val Leu Ser Asn
885 890 895

Gln Asn His Gln Trp Asp Gln Val Gly Arg Phe Phe Ser Glu Val Asp
900 905 910

Ala Asn Leu Met Leu Ala Leu Tyr Asn Asn Ser Phe Tyr Thr Arg Lys
915 920 925

Glu Ser Tyr Asp Tyr Gln Ala Ala Cys Ala Pro Gln Pro Pro Gly Asn
930 935 940

Leu Gly Ala Ala Pro Arg Gly Val Phe Val Pro Thr Val Ala Asp Phe
945 950 955 960

Leu Asn Leu Ala Trp Trp Thr Ser Ala Ala Ala Trp Ser Leu Phe Gln
965 970 975

Gln Leu Leu Tyr Gly Leu Ile Tyr His Ser Trp Phe Gln Ala Asp Pro
980 985 990

Ala Glu Ala Glu Gly Ser Pro Glu Thr Arg Glu Ser Ser Cys Val Met
995 1000 1005

Lys Gln Thr Gln Tyr Tyr Phe Gly Ser Val Asn Ala Ser Tyr Asn Ala
1010 1015 1020

Ile Ile Asp Cys Gly Asn Cys Ser Arg Leu Phe His Ala Gln Arg Leu
1025 1030 1035 1040

Thr Asn Thr Asn Leu Leu Phe Val Val Ala Glu Lys Pro Leu Cys Ser
1045 1050 1055

Gln Cys Glu Ala Gly Arg Leu Leu Gln Lys Glu Thr His Cys Pro Ala
1060 1065 1070

Asp Gly Pro Glu Gln Cys Glu Leu Val Gln Arg Pro Arg Tyr Arg Arg
1075 1080 1085

Gly Pro His Ile Cys Phe Asp Tyr Asn Ala Thr Glu Asp Thr Ser Asp
1090 1095 1100

Cys Gly Arg Gly Ala His His His His His His
1105 1110 1115

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<212> PRT
<213> Mus musculus

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35 40 45

Phe Gly Gly Glu Ile Lys Ser Ile Ala Ala Lys Tyr Ser Gly Ser Gln
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Leu Leu Gln Lys Lys Tyr Lys Glu Tyr Glu Lys Asp Val Ala Ile Glu
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Glu Ile Asp Gly Leu Gln Leu Val Lys Lys Leu Ala Lys Ile Met Glu
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Glu Met Phe His Lys Lys Ser Glu Ala Val Arg Arg Leu Val Glu Ala
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Ala Glu Glu Ala His Leu Lys His Glu Phe Asp Ala Asp Leu Gln Tyr
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Glu Tyr Phe Asn Ala Val Leu Ile Asn Glu Arg Asp Lys Asp Gly Asn
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Phe Leu Glu Leu Gly Lys Glu Phe Ile Leu Ala Pro Asn Asp His Phe

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Asn Met Tyr Asn Lys Asp Pro Ala Ile Val Asn Gly Val Tyr Trp Ser
            180                 185                 190

Glu Ser Leu Asn Lys Val Phe Val Asp Asn Phe Asp Arg Asp Pro Ser
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Leu Ile Trp Gln Tyr Phe Gly Ser Ala Lys Gly Phe Phe Arg Gln Tyr
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Pro Gly Ile Lys Trp Glu Pro Asp Glu Asn Gly Val Ile Ala Phe Asp
225                 230                 235                 240

Cys Arg Asn Arg Lys Trp Tyr Ile Gln Ala Ala Thr Ser Pro Lys Asp
                245                 250                 255

Val Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu Arg Leu
            260                 265                 270

Thr Ile Ala Lys Gln Thr Val Ser Ser Ile Leu Asp Thr Leu Gly Asp
        275                 280                 285

Asp Asp Phe Phe Asn Ile Ile Thr Tyr Asn Glu Glu Leu His Tyr Val
    290                 295                 300

Glu Pro Cys Leu Asn Gly Thr Leu Val Gln Ala Asp Arg Thr Asn Lys
305                 310                 315                 320

Glu His Phe Arg Glu His Leu Asp Lys Leu Phe Ala Lys Gly Ile Gly
                325                 330                 335

Met Leu Asp Ile Ala Leu Asn Glu Ala Phe Asn Ile Leu Ser Asp Phe
            340                 345                 350

Asn His Thr Gly Gln Gly Ser Ile Cys Ser Gln Ala Ile Met Leu Ile
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Thr Asp Gly Ala Val Asp Thr Tyr Asp Thr Ile Phe Ala Lys Tyr Asn
    370                 375                 380

Trp Pro Asp Arg Lys Val Arg Ile Phe Thr Tyr Leu Ile Gly Arg Glu
385                 390                 395                 400

Ala Ala Phe Ala Asp Asn Leu Lys Trp Met Ala Cys Ala Asn Lys Gly
                405                 410                 415

Phe Phe Thr Gln Ile Ser Thr Leu Ala Asp Val Gln Glu Asn Val Met
            420                 425                 430

Glu Tyr Leu His Val Leu Ser Arg Pro Lys Val Ile Asp Gln Glu His
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Asp Val Val Trp Thr Glu Ala Tyr Ile Asp Ser Thr Leu Pro Gln Ala
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Gln Lys Leu Ala Asp Asp Gln Gly Leu Val Leu Met Thr Thr Val Ala
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Met Pro Val Phe Ser Lys Gln Asn Glu Thr Arg Ser Lys Gly Ile Leu
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Leu Gly Val Val Gly Thr Asp Val Pro Val Lys Glu Leu Leu Lys Thr
            500                 505                 510

Ile Pro Lys Tyr Lys Leu Gly Ile His Gly Tyr Ala Phe Ala Ile Thr
        515                 520                 525

Asn Asn Gly Tyr Ile Leu Thr His Pro Glu Leu Arg Pro Leu Tyr Glu
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Glu Gly Lys Lys Arg Arg Lys Pro Asn Tyr Ser Ser Val Asp Leu Ser
545                 550                 555                 560

Glu Val Glu Trp Glu Asp Arg Asp Asp Val Leu Arg Asn Ala Met Val
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Asn Arg Lys Thr Gly Lys Phe Ser Met Glu Val Lys Lys Thr Val Asp
            580                 585                 590

Lys Gly Lys Arg Val Leu Val Met Thr Asn Asp Tyr Tyr Tyr Thr Asp
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Ile Lys Gly Thr Pro Phe Ser Leu Gly Val Ala Leu Ser Arg Gly His
    610                 615                 620

Gly Lys Tyr Phe Phe Arg Gly Asn Val Thr Ile Glu Glu Gly Leu His
625                 630                 635                 640

Asp Leu Glu His Pro Asp Val Ser Leu Ala Asp Glu Trp Ser Tyr Cys
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Asn Thr Asp Leu His Pro Glu His Arg His Leu Ser Gln Leu Glu Ala
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Ile Lys Leu Tyr Leu Lys Gly Lys Glu Pro Leu Leu Gln Cys Asp Lys
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Glu Leu Ile Gln Glu Val Leu Phe Asp Ala Val Val Ser Ala Pro Ile
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Glu Ala Tyr Trp Thr Ser Leu Ala Leu Asn Lys Ser Glu Asn Ser Asp
705                 710                 715                 720

Lys Gly Val Glu Val Ala Phe Leu Gly Thr Arg Thr Gly Leu Ser Arg
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Ile Asn Leu Phe Val Gly Ala Glu Gln Leu Thr Asn Gln Asp Phe Leu
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Lys Ala Gly Asp Lys Glu Asn Ile Phe Asn Ala Asp His Phe Pro Leu
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Trp Tyr Arg Arg Ala Ala Glu Gln Ile Ala Gly Ser Phe Val Tyr Ser
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Ser Thr Ser Ile Gln Leu Leu Asp Glu Arg Lys Ser Pro Val Val Ala
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Ala Val Gly Ile Gln Met Lys Leu Glu Phe Phe Gln Arg Lys Phe Trp
            820                 825                 830

Thr Ala Ser Arg Gln Cys Ala Ser Leu Asp Gly Lys Cys Ser Ile Ser
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Cys Asp Asp Glu Thr Val Asn Cys Tyr Leu Ile Asp Asn Asn Gly Phe
    850                 855                 860

Ile Leu Val Ser Glu Asp Tyr Thr Gln Thr Gly Asp Phe Phe Gly Glu
865                 870                 875                 880

Val Glu Gly Ala Val Met Asn Lys Leu Leu Thr Met Gly Ser Phe Lys
                885                 890                 895

Arg Ile Thr Leu Tyr Asp Tyr Gln Ala Met Cys Arg Ala Asn Lys Glu
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Ser Ser Asp Ser Ala His Gly Leu Leu Asp Pro Tyr Lys Ala Phe Leu
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Ser Ala Ala Lys Trp Ile Met Thr Glu Leu Val Leu Phe Leu Val Glu
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Phe Asn Leu Cys Ser Trp Trp His Ser Asp Met Thr Ala Lys Ala Gln
945                 950                 955                 960

Lys Leu Lys Gln Thr Leu Glu Pro Cys Asp Thr Glu Tyr Pro Ala Phe
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Val Ser Glu Arg Thr Ile Lys Glu Thr Thr Gly Asn Ile Ala Cys Glu
            980                 985                 990

Asp Cys Ser Lys Ser Phe Val Ile Gln Gln Ile Pro Ser Ser Asn Leu
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Phe Met Val Val Val Asp Ser Ser Cys Leu Cys Glu Ser Val Ala Pro
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Ile Thr Met Ala Pro Ile Glu Ile Arg Tyr Asn Glu Ser Leu Lys Cys
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Glu Arg Leu Lys Ala Gln Lys Ile Arg Arg Arg Pro Glu Ser Cys His
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Gly Phe His Pro Glu Glu Asn Ala Arg Glu Cys Gly Gly Ala Ser His
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His His His His His
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<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

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<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 27
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<210> 28
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<212> DNA
<213> Artificial Sequence

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<223> Description of Artificial Sequence: primer

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<211> 3842
<212> DNA
<213> Sus scrofa

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ttaatattca taatggttga gagcaaaggg acttgtcctt gtgacacacg attgctcata 3060
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35 40 45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
50 55 60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65 70 75 80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
85 90 95

Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
100 105 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
115 120 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
130 135 140

Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
145 150 155 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
165 170 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
180 185 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
195 200 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
210 215 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225 230 235 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile

245 250 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
260 265 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
275 280 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
290 295 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305 310 315 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
325 330 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
340 345 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
355 360 365

Ala Gln Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
370 375 380

Phe Thr Phe Ser Val Gly Gln His Asn Tyr Asp Arg Gly Pro Ile Gln
385 390 395 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
405 410 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
420 425 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
435 440 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
450 455 460

Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys
465 470 475 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
485 490 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
500 505 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
515 520 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
530 535 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
545 550 555 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
595 600 605

Phe Tyr Tyr Ile Lys Ala Lys Ile Glu Glu Thr Ile Thr Gln Ala Arg
610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625 630 635 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp
675 680 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705 710 715 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
755 760 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865 870 875 880

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Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
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Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Ile
            900                 905                 910

Ala Asp Ile Leu His Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
        915                 920                 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
    930                 935                 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945                 950                 955                 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
                965                 970                 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
            980                 985                 990

Val Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
        995                1000                1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
   1010                1015                1020

Thr Ser Asp Gly Pro Asp Pro Cys Asp Met Val Lys Gln Pro Arg Tyr
1025                1030                1035                1040

Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn Ala Leu Glu Asp Tyr
                1045                1050                1055

Thr Asp Cys Gly Gly Val Ser Gly Leu Asn Pro Ser Leu Trp Ser Ile
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Phe Gly Ile Gln Cys Val Leu Leu Trp Leu Leu Ser Gly Ser Arg His
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Tyr Gln Leu
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Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
        35                  40                  45
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Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
50 55 60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65 70 75 80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
85 90 95

Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
100 105 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
115 120 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
130 135 140

Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
145 150 155 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
165 170 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
180 185 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
195 200 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
210 215 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225 230 235 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
245 250 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
260 265 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
275 280 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
290 295 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305 310 315 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
325 330 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
340 345 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
355 360 365

Ala Gln Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
370 375 380

Phe Thr Phe Ser Val Gly Gln His Asn Tyr Asp Arg Gly Pro Ile Gln
385 390 395 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
405 410 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
420 425 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
435 440 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
450 455 460

Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys
465 470 475 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
485 490 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
500 505 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
515 520 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
530 535 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
545 550 555 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
595 600 605

Phe Tyr Tyr Ile Lys Ala Lys Ile Glu Glu Thr Ile Thr Gln Ala Arg
610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625 630 635 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp

675 680 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705 710 715 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
755 760 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
885 890 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Ile
900 905 910

Ala Asp Ile Leu His Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
915 920 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
930 935 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945 950 955 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
965 970 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
980 985 990

Val Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
995 1000 1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu
1010 1015

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35 40 45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
50 55 60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65 70 75 80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
85 90 95

Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
100 105 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
115 120 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
130 135 140

Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
145 150 155 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
165 170 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
180 185 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
195 200 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
210 215 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225 230 235 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile

245 250 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
260 265 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
275 280 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
290 295 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305 310 315 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
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Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
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Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
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Ala Gln Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
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Phe Thr Phe Ser Val Gly Gln His Asn Tyr Asp Arg Gly Pro Ile Gln
385 390 395 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
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Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
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Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
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Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
450 455 460

Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys
465 470 475 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
485 490 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
500 505 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
515 520 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
530 535 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
545 550 555 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
595 600 605

Phe Tyr Tyr Ile Lys Ala Lys Ile Glu Glu Thr Ile Thr Gln Ala Arg
610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625 630 635 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp
675 680 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705 710 715 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
755 760 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
885 890 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Ile
900 905 910

Ala Asp Ile Leu His Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
915 920 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
930 935 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945 950 955 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
965 970 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
980 985 990

Val Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
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Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
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Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
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Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
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Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
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Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
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Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
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Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
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Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
145 150 155 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
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Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
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Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
195 200 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
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Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
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Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
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Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
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Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
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355 360 365

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Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
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Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
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Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
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465 470 475 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
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Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
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Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
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Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
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Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
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Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
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Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
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675 680 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
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Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
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Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
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Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
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Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
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Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
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Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
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Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
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Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
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Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
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Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
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Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
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Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
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Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
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Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
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Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys
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Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
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Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
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Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp
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Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Ile
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Val Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
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Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
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aaagtacgtg tattcaggtt ttcagttggt caacacaatt atgagagagg acctattcag 1200
tggatggcct gtgaaaacaa aggttattat tatgaaattc cttccattgg tgcaataaga 1260
atcaatactc aggaatattt ggatgttttg ggaagaccaa tggttttagc aggagacaaa 1320
gctaagcaag tccaatggac aaatgtgtac ctggatgcat tggaactggg acttgtcatt 1380
actggaactc ttccggtctt caacataacc ggccaatttg aaaataagac aaacttaaag 1440
aaccagctga ttcttggtgt gatgggagta gatgtgtctt tggaagatat taaaagactg 1500
acaccacgtt ttacactgtg ccccaatggg tattactttg caatcgatcc taatggttat 1560
gttttattac atccaaatct tcagccaaag aaccccaaat ctcaggagcc agtaacattg 1620
gatttccttg atgcagagtt agagaatgat attaaagtgg agattcgaaa taagatgatt 1680
gatggggaaa gtggagaaaa aacattcaga actctggtta aatctcaaga tgagagatat 1740
attgacaaag gaaacaggac atacacatgg acacctgtca atggcacaga ttacagtttg 1800
gccttggtat taccaaccta cagtttttac tatataaaag ccaaactaga agagacaata 1860
actcaggcca gatcaaaaaa gggcaaaatg aaggattcgg aaaccctgaa gccagataat 1920
tttgaagaat ctggctatac attcatagca ccaagagatt actgcaatga cctgaaaata 1980
tcggataata acactgaatt tcttttaaat ttcaacgagt ttattgatag aaaaactcca 2040
aacaacccat catgtaacgc ggatttgatt aatagagtct tgcttgatgc aggctttaca 2100
aatgaacttg tccaaaatta ctggagtaag cagaaaaata tcaagggagt gaaagcacga 2160
tttgttgtga ctgatggtgg gattaccaga gtttatccca aagaggctgg agaaaattgg 2220
caagaaaacc cagagacata tgaggacagc ttctataaaa ggagcctaga taatgataac 2280
tatgttttca ctgctcccta ctttaacaaa agtggacctg gtgcctatga atcgggcatt 2340
atggtaagca aagctgtaga aatatatatt caagggaaac ttcttaaacc tgcagttgtt 2400
ggaattaaaa ttgatgtaaa ttcctggata gagaatttca ccaaaacctc aatcagagat 2460
ccgtgtgctg gtccagtttg tgactgcaaa agaaacagtg acgtaatgga ttgtgtgatt 2520
ctggatgatg gtgggtttct tctgatggca aatcatgatg attatactaa tcagattgga 2580
agatttttg gagagattga tcccagcttg atgagacacc tggttaatat atcagtttat 2640
gcttttaaca aatcttatga ttatcagtca gtatgtgagc ccggtgctgc accaaaacaa 2700
ggagcaggac atcgctcagc atatgtgcca tcagtagcag acatattaca aattggctgg 2760
tgggccactg ctgctgcctg gtctattcta cagcagtttc tcttgagttt gacctttcca 2820
cgactccttg aggcagttga gatggaggat gatgacttca cggcctccct gtccaagcag 2880
agctgcatta ctgaacaaac ccagtatttc ttcgataacg acagtaaatc attcagtggt 2940
gtattagact gtggaaactg ttccagaatc tttcatggag aaaagcttat gaacaccaac 3000
ttaatattca taatggttga gagcaaaggg acatgtccat gtgacacacg actgctcata 3060
caagcggagc agacttctga cggtccaaat ccttgtgaca tggttaagca acctagatac 3120
cgaaaagggc ctgatgtctg ctttgataac aatgtcttgg aggattatac tgactgtggt 3180
ggtgtttctg 3190

<210> 41
<211> 1018
<212> PRT
<213> Homo sapiens

<400> 41
Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser
1 5 10 15

Leu Leu Ile Gly Pro Ser Ser Glu Glu Pro Phe Pro Ser Ala Val Thr
20 25 30

Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
35 40 45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
50 55 60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65 70 75 80

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Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
                85                  90                  95

Leu Val Ser Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
            100                 105                 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
        115                 120                 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
    130                 135                 140

Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser
145                 150                 155                 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
                165                 170                 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
            180                 185                 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
        195                 200                 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
    210                 215                 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225                 230                 235                 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
                245                 250                 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
            260                 265                 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
        275                 280                 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
    290                 295                 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305                 310                 315                 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
                325                 330                 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
            340                 345                 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
        355                 360                 365

Ala Gln Glu Ile Phe Asn Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
    370                 375                 380

Phe Arg Phe Ser Val Gly Gln His Asn Tyr Glu Arg Gly Pro Ile Gln
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385 390 395 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
405 410 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
420 425 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
435 440 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
450 455 460

Pro Val Phe Asn Ile Thr Gly Gln Phe Glu Asn Lys Thr Asn Leu Lys
465 470 475 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
485 490 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
500 505 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
515 520 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
530 535 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
545 550 555 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
595 600 605

Phe Tyr Tyr Ile Lys Ala Lys Leu Glu Glu Thr Ile Thr Gln Ala Arg
610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625 630 635 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp
675 680 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705 710 715 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
755 760 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
885 890 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Val
900 905 910

Ala Asp Ile Leu Gln Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
915 920 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
930 935 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945 950 955 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
965 970 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
980 985 990

Gly Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
995 1000 1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu
1010 1015

<210> 42
<211> 1036
<212> PRT
<213> Homo sapiens

<400> 42

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Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser
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Leu Leu Ile Gly Pro Ser Ser Glu Glu Pro Phe Pro Ser Ala Val Thr
            20                  25                  30

Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
        35                  40                  45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
    50                  55                  60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65                  70                  75                  80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
                85                  90                  95

Leu Val Ser Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
            100                 105                 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
        115                 120                 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
    130                 135                 140

Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser
145                 150                 155                 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
                165                 170                 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
            180                 185                 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
        195                 200                 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
    210                 215                 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225                 230                 235                 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
                245                 250                 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
            260                 265                 270
```

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
275 280 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
290 295 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305 310 315 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
325 330 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
340 345 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
355 360 365

Ala Gln Glu Ile Phe Asn Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
370 375 380

Phe Arg Phe Ser Val Gly Gln His Asn Tyr Glu Arg Gly Pro Ile Gln
385 390 395 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
405 410 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
420 425 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
435 440 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
450 455 460

Pro Val Phe Asn Ile Thr Gly Gln Phe Glu Asn Lys Thr Asn Leu Lys
465 470 475 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
485 490 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
500 505 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
515 520 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
530 535 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
545 550 555 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
595 600 605

Phe Tyr Tyr Ile Lys Ala Lys Leu Glu Glu Thr Ile Thr Gln Ala Arg
610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625 630 635 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp
675 680 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705 710 715 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
755 760 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
885 890 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Val

900 905 910

Ala Asp Ile Leu Gln Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
915 920 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
930 935 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945 950 955 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
965 970 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
980 985 990

Gly Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
995 1000 1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
1010 1015 1020

Thr Ser Asp Gly Pro Asn Pro Cys Asp Met Val Lys
1025 1030 1035

<210> 43
<211> 1063
<212> PRT
<213> Homo sapiens

<400> 43
Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser
1 5 10 15

Leu Leu Ile Gly Pro Ser Ser Glu Glu Pro Phe Pro Ser Ala Val Thr
20 25 30

Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
35 40 45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
50 55 60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65 70 75 80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
85 90 95

Leu Val Ser Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
100 105 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
115 120 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
130 135 140

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Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser
145                 150                 155                 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
                165                 170                 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
            180                 185                 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
        195                 200                 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
    210                 215                 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225                 230                 235                 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
                245                 250                 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
            260                 265                 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
        275                 280                 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
    290                 295                 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305                 310                 315                 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
                325                 330                 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
            340                 345                 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
        355                 360                 365

Ala Gln Glu Ile Phe Asn Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
    370                 375                 380

Phe Arg Phe Ser Val Gly Gln His Asn Tyr Glu Arg Gly Pro Ile Gln
385                 390                 395                 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
                405                 410                 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
            420                 425                 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
        435                 440                 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
```

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    450                 455                 460

Pro Val Phe Asn Ile Thr Gly Gln Phe Glu Asn Lys Thr Asn Leu Lys
465                 470                 475                 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
                485                 490                 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
            500                 505                 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
        515                 520                 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
    530                 535                 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
545                 550                 555                 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
                565                 570                 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
            580                 585                 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
        595                 600                 605

Phe Tyr Tyr Ile Lys Ala Lys Leu Glu Glu Thr Ile Thr Gln Ala Arg
    610                 615                 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625                 630                 635                 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
                645                 650                 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
            660                 665                 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp
        675                 680                 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
    690                 695                 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705                 710                 715                 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
                725                 730                 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
            740                 745                 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
        755                 760                 765
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Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
    770                 775                 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785                 790                 795                 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
                805                 810                 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
            820                 825                 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
        835                 840                 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
    850                 855                 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865                 870                 875                 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
                885                 890                 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Val
            900                 905                 910

Ala Asp Ile Leu Gln Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
        915                 920                 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
    930                 935                 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945                 950                 955                 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
                965                 970                 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
            980                 985                 990

Gly Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
        995                1000                1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
   1010                1015                1020

Thr Ser Asp Gly Pro Asn Pro Cys Asp Met Val Lys Gln Pro Arg Tyr
1025                1030                1035                1040

Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn Val Leu Glu Asp Tyr
                1045                1050                1055

Thr Asp Cys Gly Gly Val Ser
            1060
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<210> 44

<211> 1091
<212> PRT
<213> Homo sapiens

<400> 44

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Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser
  1               5                  10                  15

Leu Leu Ile Gly Pro Ser Ser Glu Glu Pro Phe Pro Ser Ala Val Thr
             20                  25                  30

Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
         35                  40                  45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
     50                  55                  60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
 65                  70                  75                  80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
                 85                  90                  95

Leu Val Ser Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
            100                 105                 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
        115                 120                 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
    130                 135                 140

Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser
145                 150                 155                 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
                165                 170                 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
            180                 185                 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
        195                 200                 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
    210                 215                 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225                 230                 235                 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
                245                 250                 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
            260                 265                 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
        275                 280                 285
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Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
290 295 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305 310 315 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
325 330 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
340 345 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
355 360 365

Ala Gln Glu Ile Phe Asn Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
370 375 380

Phe Arg Phe Ser Val Gly Gln His Asn Tyr Glu Arg Gly Pro Ile Gln
385 390 395 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
405 410 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
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Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
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Pro Val Phe Asn Ile Thr Gly Gln Phe Glu Asn Lys Thr Asn Leu Lys
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Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
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Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
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Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
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Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
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Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
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Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
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Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
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Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
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Phe Tyr Tyr Ile Lys Ala Lys Leu Glu Glu Thr Ile Thr Gln Ala Arg
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Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
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Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
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Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp
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Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
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Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
725 730 735

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Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
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Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
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915 920 925

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tcttcacgga catcagcgac acccctttca gtttgggggt ggtgctgtcc cggggccacg 1920
gagaatacat ccttctgggg aacacgtctg tggaagaagg cctgcatgac ttgcttcacc 1980
cagacctggc cctggccggt gactggatct actgcatcac agatattgac ccagaccacc 2040
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catccagagg agaatgccca ggactgcggc ggcgcctcg 3339

<210> 53
<211> 1050
<212> PRT
<213> Homo sapiens

<400> 53
Met Pro Ala Thr Pro Asn Phe Leu Ala Asn Pro Ser Ser Ser Ser Arg
1 5 10 15

Trp Ile Pro Leu Gln Pro Met Pro Val Ala Trp Ala Phe Val Gln Lys
20 25 30

Thr Ser Ala Leu Leu Trp Leu Leu Leu Leu Gly Thr Ser Leu Ser Pro
35 40 45

```
Ala Trp Gly Gln Ala Lys Ile Pro Leu Glu Thr Val Lys Leu Trp Ala
     50                  55                  60

Asp Thr Phe Gly Gly Asp Leu Tyr Asn Thr Val Thr Lys Tyr Ser Gly
 65                  70                  75                  80

Ser Leu Leu Leu Gln Lys Lys Tyr Lys Asp Val Glu Ser Ser Leu Lys
                 85                  90                  95

Ile Glu Glu Val Asp Gly Leu Glu Leu Val Arg Lys Phe Ser Glu Asp
            100                 105                 110

Met Glu Asn Met Leu Arg Arg Lys Val Glu Ala Val Gln Asn Leu Val
        115                 120                 125

Glu Ala Ala Glu Glu Ala Asp Leu Asn His Glu Phe Asn Glu Ser Leu
    130                 135                 140

Val Phe Asp Tyr Tyr Asn Ser Val Leu Ile Asn Glu Arg Asp Glu Lys
145                 150                 155                 160

Gly Asn Phe Val Glu Leu Gly Ala Glu Phe Leu Leu Glu Ser Asn Ala
                165                 170                 175

His Phe Ser Asn Leu Pro Val Asn Thr Ser Ile Ser Ser Val Gln Leu
            180                 185                 190

Pro Thr Asn Val Tyr Asn Lys Asp Pro Asp Ile Leu Asn Gly Val Tyr
        195                 200                 205

Met Ser Glu Ala Leu Asn Ala Val Phe Val Glu Asn Phe Gln Arg Asp
    210                 215                 220

Pro Thr Leu Thr Trp Gln Tyr Phe Gly Ser Ala Thr Gly Phe Phe Arg
225                 230                 235                 240

Ile Tyr Pro Gly Ile Lys Trp Thr Pro Asp Glu Asn Gly Val Ile Thr
                245                 250                 255

Phe Asp Cys Arg Asn Arg Gly Trp Tyr Ile Gln Ala Ala Thr Ser Pro
            260                 265                 270

Lys Asp Ile Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu
        275                 280                 285

Arg Met Thr Ile Ala Lys His Thr Ile Thr Thr Ile Leu Asp Thr Leu
    290                 295                 300

Gly Glu Asn Asp Phe Val Asn Ile Ile Ala Tyr Asn Asp Tyr Val His
305                 310                 315                 320

Tyr Ile Glu Pro Cys Phe Lys Gly Ile Leu Val Gln Ala Asp Arg Asp
                325                 330                 335

Asn Arg Glu His Phe Lys Leu Leu Val Glu Glu Leu Met Val Lys Gly
            340                 345                 350

Val Gly Val Val Asp Gln Ala Leu Arg Glu Ala Phe Gln Ile Leu Lys
```

```
        355                 360                 365

Gln Phe Gln Glu Ala Lys Gln Gly Ser Leu Cys Asn Gln Ala Ile Met
    370                 375                 380

Leu Ile Ser Asp Gly Ala Val Glu Asp Tyr Glu Pro Val Phe Glu Lys
385                 390                 395                 400

Tyr Asn Trp Pro Asp Cys Lys Val Arg Val Phe Thr Tyr Leu Ile Gly
                405                 410                 415

Arg Glu Val Ser Phe Ala Asp Arg Met Lys Trp Ile Ala Cys Asn Asn
            420                 425                 430

Lys Gly Tyr Tyr Thr Gln Ile Ser Thr Leu Ala Asp Thr Gln Glu Asn
        435                 440                 445

Val Met Glu Tyr Leu His Val Leu Ser Arg Pro Met Val Ile Asn His
    450                 455                 460

Asp His Asp Ile Ile Trp Thr Glu Ala Tyr Met Asp Ser Lys Leu Leu
465                 470                 475                 480

Ser Ser Gln Ala Gln Ser Leu Thr Leu Leu Thr Thr Val Ala Met Pro
                485                 490                 495

Val Phe Ser Lys Lys Asn Glu Thr Arg Ser His Gly Ile Leu Leu Gly
            500                 505                 510

Val Val Gly Ser Asp Val Ala Leu Arg Glu Leu Met Lys Leu Ala Pro
        515                 520                 525

Arg Tyr Lys Leu Gly Val His Gly Tyr Ala Phe Leu Asn Thr Asn Asn
    530                 535                 540

Gly Tyr Ile Leu Ser His Pro Asp Leu Arg Pro Leu Tyr Arg Glu Gly
545                 550                 555                 560

Lys Lys Leu Lys Pro Lys Pro Asn Tyr Asn Ser Val Asp Leu Ser Glu
                565                 570                 575

Val Glu Trp Glu Asp Gln Ala Glu Ser Leu Arg Thr Ala Met Ile Asn
            580                 585                 590

Arg Glu Thr Gly Thr Leu Ser Met Asp Val Lys Val Pro Met Asp Lys
        595                 600                 605

Gly Lys Arg Val Leu Phe Leu Thr Asn Asp Tyr Phe Phe Thr Asp Ile
    610                 615                 620

Ser Asp Thr Pro Phe Ser Leu Gly Val Val Leu Ser Arg Gly His Gly
625                 630                 635                 640

Glu Tyr Ile Leu Leu Gly Asn Thr Ser Val Glu Glu Gly Leu His Asp
                645                 650                 655

Leu Leu His Pro Asp Leu Ala Leu Ala Gly Asp Trp Ile Tyr Cys Ile
            660                 665                 670
```

Thr Asp Ile Asp Pro Asp His Arg Lys Leu Ser Gln Leu Glu Ala Met
675 680 685

Ile Arg Phe Leu Thr Arg Lys Asp Pro Asp Leu Glu Cys Asp Glu Glu
690 695 700

Leu Val Arg Glu Val Leu Phe Asp Ala Val Val Thr Ala Pro Met Glu
705 710 715 720

Ala Tyr Trp Thr Ala Leu Ala Leu Asn Met Ser Glu Glu Ser Glu His
725 730 735

Val Val Asp Met Ala Phe Leu Gly Thr Arg Ala Gly Leu Leu Arg Ser
740 745 750

Ser Leu Phe Val Gly Ser Glu Lys Val Ser Asp Arg Lys Phe Leu Thr
755 760 765

Pro Glu Asp Glu Ala Ser Val Phe Thr Leu Asp Arg Phe Pro Leu Trp
770 775 780

Tyr Arg Gln Ala Ser Glu His Pro Ala Gly Ser Phe Val Phe Asn Leu
785 790 795 800

Arg Trp Ala Glu Gly Pro Glu Ser Ala Gly Glu Pro Met Val Val Thr
805 810 815

Ala Ser Thr Ala Val Ala Val Thr Val Asp Lys Arg Thr Ala Ile Ala
820 825 830

Ala Ala Ala Gly Val Gln Met Lys Leu Glu Phe Leu Gln Arg Lys Phe
835 840 845

Trp Ala Ala Thr Arg Gln Cys Ser Thr Val Asp Gly Pro Cys Thr Gln
850 855 860

Ser Cys Glu Asp Ser Asp Leu Asp Cys Phe Val Ile Asp Asn Asn Gly
865 870 875 880

Phe Ile Leu Ile Ser Lys Arg Ser Arg Glu Thr Gly Arg Phe Leu Gly
885 890 895

Glu Val Asp Gly Ala Val Leu Thr Gln Leu Leu Ser Met Gly Val Phe
900 905 910

Ser Gln Val Thr Met Tyr Asp Tyr Gln Ala Met Cys Lys Pro Ser Ser
915 920 925

His His His Ser Ala Ala Gln Pro Leu Val Ser Pro Ile Ser Ala Phe
930 935 940

Leu Thr Ala Thr Arg Trp Leu Leu Gln Glu Leu Val Leu Phe Leu Leu
945 950 955 960

Glu Trp Ser Val Trp Gly Ser Trp Tyr Asp Arg Gly Ala Glu Ala Lys
965 970 975

Ser Val Phe His His Ser His Lys His Lys Lys Gln Asp Pro Leu Gln
980 985 990

```
Pro Cys Asp Thr Glu Tyr Pro Val Phe Val Tyr Gln Pro Ala Ile Arg
        995                1000                1005

Glu Ala Asn Gly Ile Val Glu Cys Gly Pro Cys Gln Lys Val Phe Val
   1010                1015                1020

Val Gln Gln Ile Pro Asn Ser Asn Leu Leu Leu Leu Val Thr Asp Pro
1025                1030                1035                1040

Thr Cys Asp Cys Ser Ile Phe Pro Pro Val
                1045                1050
```

<210> 54
<211> 1069
<212> PRT
<213> Homo sapiens

<400> 54

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Met Pro Ala Thr Pro Asn Phe Leu Ala Asn Pro Ser Ser Ser Ser Arg
  1               5                  10                  15

Trp Ile Pro Leu Gln Pro Met Pro Val Ala Trp Ala Phe Val Gln Lys
             20                  25                  30

Thr Ser Ala Leu Leu Trp Leu Leu Leu Leu Gly Thr Ser Leu Ser Pro
         35                  40                  45

Ala Trp Gly Gln Ala Lys Ile Pro Leu Glu Thr Val Lys Leu Trp Ala
     50                  55                  60

Asp Thr Phe Gly Gly Asp Leu Tyr Asn Thr Val Thr Lys Tyr Ser Gly
 65                  70                  75                  80

Ser Leu Leu Leu Gln Lys Lys Tyr Lys Asp Val Glu Ser Ser Leu Lys
                 85                  90                  95

Ile Glu Glu Val Asp Gly Leu Glu Leu Val Arg Lys Phe Ser Glu Asp
            100                 105                 110

Met Glu Asn Met Leu Arg Arg Lys Val Glu Ala Val Gln Asn Leu Val
        115                 120                 125

Glu Ala Ala Glu Glu Ala Asp Leu Asn His Glu Phe Asn Glu Ser Leu
    130                 135                 140

Val Phe Asp Tyr Tyr Asn Ser Val Leu Ile Asn Glu Arg Asp Glu Lys
145                 150                 155                 160

Gly Asn Phe Val Glu Leu Gly Ala Glu Phe Leu Leu Glu Ser Asn Ala
                165                 170                 175

His Phe Ser Asn Leu Pro Val Asn Thr Ser Ile Ser Ser Val Gln Leu
            180                 185                 190

Pro Thr Asn Val Tyr Asn Lys Asp Pro Asp Ile Leu Asn Gly Val Tyr
        195                 200                 205
```

```
Met Ser Glu Ala Leu Asn Ala Val Phe Val Glu Asn Phe Gln Arg Asp
    210                 215                 220

Pro Thr Leu Thr Trp Gln Tyr Phe Gly Ser Ala Thr Gly Phe Phe Arg
225                 230                 235                 240

Ile Tyr Pro Gly Ile Lys Trp Thr Pro Asp Glu Asn Gly Val Ile Thr
                245                 250                 255

Phe Asp Cys Arg Asn Arg Gly Trp Tyr Ile Gln Ala Ala Thr Ser Pro
            260                 265                 270

Lys Asp Ile Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu
        275                 280                 285

Arg Met Thr Ile Ala Lys His Thr Ile Thr Thr Ile Leu Asp Thr Leu
    290                 295                 300

Gly Glu Asn Asp Phe Val Asn Ile Ile Ala Tyr Asn Asp Tyr Val His
305                 310                 315                 320

Tyr Ile Glu Pro Cys Phe Lys Gly Ile Leu Val Gln Ala Asp Arg Asp
                325                 330                 335

Asn Arg Glu His Phe Lys Leu Leu Val Glu Glu Leu Met Val Lys Gly
            340                 345                 350

Val Gly Val Val Asp Gln Ala Leu Arg Glu Ala Phe Gln Ile Leu Lys
        355                 360                 365

Gln Phe Gln Glu Ala Lys Gln Gly Ser Leu Cys Asn Gln Ala Ile Met
    370                 375                 380

Leu Ile Ser Asp Gly Ala Val Glu Asp Tyr Glu Pro Val Phe Glu Lys
385                 390                 395                 400

Tyr Asn Trp Pro Asp Cys Lys Val Arg Val Phe Thr Tyr Leu Ile Gly
                405                 410                 415

Arg Glu Val Ser Phe Ala Asp Arg Met Lys Trp Ile Ala Cys Asn Asn
            420                 425                 430

Lys Gly Tyr Tyr Thr Gln Ile Ser Thr Leu Ala Asp Thr Gln Glu Asn
        435                 440                 445

Val Met Glu Tyr Leu His Val Leu Ser Arg Pro Met Val Ile Asn His
    450                 455                 460

Asp His Asp Ile Ile Trp Thr Glu Ala Tyr Met Asp Ser Lys Leu Leu
465                 470                 475                 480

Ser Ser Gln Ala Gln Ser Leu Thr Leu Leu Thr Thr Val Ala Met Pro
                485                 490                 495

Val Phe Ser Lys Lys Asn Glu Thr Arg Ser His Gly Ile Leu Leu Gly
            500                 505                 510

Val Val Gly Ser Asp Val Ala Leu Arg Glu Leu Met Lys Leu Ala Pro
        515                 520                 525
```

Arg Tyr Lys Leu Gly Val His Gly Tyr Ala Phe Leu Asn Thr Asn Asn
530 535 540

Gly Tyr Ile Leu Ser His Pro Asp Leu Arg Pro Leu Tyr Arg Glu Gly
545 550 555 560

Lys Lys Leu Lys Pro Lys Pro Asn Tyr Asn Ser Val Asp Leu Ser Glu
565 570 575

Val Glu Trp Glu Asp Gln Ala Glu Ser Leu Arg Thr Ala Met Ile Asn
580 585 590

Arg Glu Thr Gly Thr Leu Ser Met Asp Val Lys Val Pro Met Asp Lys
595 600 605

Gly Lys Arg Val Leu Phe Leu Thr Asn Asp Tyr Phe Phe Thr Asp Ile
610 615 620

Ser Asp Thr Pro Phe Ser Leu Gly Val Val Leu Ser Arg Gly His Gly
625 630 635 640

Glu Tyr Ile Leu Leu Gly Asn Thr Ser Val Glu Glu Gly Leu His Asp
645 650 655

Leu Leu His Pro Asp Leu Ala Leu Ala Gly Asp Trp Ile Tyr Cys Ile
660 665 670

Thr Asp Ile Asp Pro Asp His Arg Lys Leu Ser Gln Leu Glu Ala Met
675 680 685

Ile Arg Phe Leu Thr Arg Lys Asp Pro Asp Leu Glu Cys Asp Glu Glu
690 695 700

Leu Val Arg Glu Val Leu Phe Asp Ala Val Val Thr Ala Pro Met Glu
705 710 715 720

Ala Tyr Trp Thr Ala Leu Ala Leu Asn Met Ser Glu Glu Ser Glu His
725 730 735

Val Val Asp Met Ala Phe Leu Gly Thr Arg Ala Gly Leu Leu Arg Ser
740 745 750

Ser Leu Phe Val Gly Ser Glu Lys Val Ser Asp Arg Lys Phe Leu Thr
755 760 765

Pro Glu Asp Glu Ala Ser Val Phe Thr Leu Asp Arg Phe Pro Leu Trp
770 775 780

Tyr Arg Gln Ala Ser Glu His Pro Ala Gly Ser Phe Val Phe Asn Leu
785 790 795 800

Arg Trp Ala Glu Gly Pro Glu Ser Ala Gly Glu Pro Met Val Val Thr
805 810 815

Ala Ser Thr Ala Val Ala Val Thr Val Asp Lys Arg Thr Ala Ile Ala
820 825 830

Ala Ala Ala Gly Val Gln Met Lys Leu Glu Phe Leu Gln Arg Lys Phe

```
        835                 840                 845

Trp Ala Ala Thr Arg Gln Cys Ser Thr Val Asp Gly Pro Cys Thr Gln
    850                 855                 860

Ser Cys Glu Asp Ser Asp Leu Asp Cys Phe Val Ile Asp Asn Asn Gly
865                 870                 875                 880

Phe Ile Leu Ile Ser Lys Arg Ser Arg Glu Thr Gly Arg Phe Leu Gly
                885                 890                 895

Glu Val Asp Gly Ala Val Leu Thr Gln Leu Leu Ser Met Gly Val Phe
            900                 905                 910

Ser Gln Val Thr Met Tyr Asp Tyr Gln Ala Met Cys Lys Pro Ser Ser
        915                 920                 925

His His His Ser Ala Ala Gln Pro Leu Val Ser Pro Ile Ser Ala Phe
    930                 935                 940

Leu Thr Ala Thr Arg Trp Leu Leu Gln Glu Leu Val Leu Phe Leu Leu
945                 950                 955                 960

Glu Trp Ser Val Trp Gly Ser Trp Tyr Asp Arg Gly Ala Glu Ala Lys
                965                 970                 975

Ser Val Phe His His Ser His Lys His Lys Lys Gln Asp Pro Leu Gln
            980                 985                 990

Pro Cys Asp Thr Glu Tyr Pro Val Phe Val Tyr Gln Pro Ala Ile Arg
        995                1000                1005

Glu Ala Asn Gly Ile Val Glu Cys Gly Pro Cys Gln Lys Val Phe Val
   1010                1015                1020

Val Gln Gln Ile Pro Asn Ser Asn Leu Leu Leu Leu Val Thr Asp Pro
1025                1030                1035                1040

Thr Cys Asp Cys Ser Ile Phe Pro Pro Val Leu Gln Glu Ala Thr Glu
                1045                1050                1055

Val Lys Tyr Asn Ala Ser Val Lys Cys Asp Arg Met Arg
            1060                1065
```

<210> 55
<211> 1097
<212> PRT
<213> Homo sapiens

<400> 55

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Met Pro Ala Thr Pro Asn Phe Leu Ala Asn Pro Ser Ser Ser Ser Arg
  1               5                  10                  15

Trp Ile Pro Leu Gln Pro Met Pro Val Ala Trp Ala Phe Val Gln Lys
             20                  25                  30

Thr Ser Ala Leu Leu Trp Leu Leu Leu Leu Gly Thr Ser Leu Ser Pro
         35                  40                  45
```

```
Ala Trp Gly Gln Ala Lys Ile Pro Leu Glu Thr Val Lys Leu Trp Ala
     50                  55                  60

Asp Thr Phe Gly Gly Asp Leu Tyr Asn Thr Val Thr Lys Tyr Ser Gly
 65                  70                  75                  80

Ser Leu Leu Leu Gln Lys Lys Tyr Lys Asp Val Glu Ser Ser Leu Lys
                 85                  90                  95

Ile Glu Glu Val Asp Gly Leu Glu Leu Val Arg Lys Phe Ser Glu Asp
            100                 105                 110

Met Glu Asn Met Leu Arg Arg Lys Val Glu Ala Val Gln Asn Leu Val
        115                 120                 125

Glu Ala Ala Glu Glu Ala Asp Leu Asn His Glu Phe Asn Glu Ser Leu
    130                 135                 140

Val Phe Asp Tyr Tyr Asn Ser Val Leu Ile Asn Glu Arg Asp Glu Lys
145                 150                 155                 160

Gly Asn Phe Val Glu Leu Gly Ala Glu Phe Leu Leu Glu Ser Asn Ala
                165                 170                 175

His Phe Ser Asn Leu Pro Val Asn Thr Ser Ile Ser Ser Val Gln Leu
            180                 185                 190

Pro Thr Asn Val Tyr Asn Lys Asp Pro Asp Ile Leu Asn Gly Val Tyr
        195                 200                 205

Met Ser Glu Ala Leu Asn Ala Val Phe Val Glu Asn Phe Gln Arg Asp
    210                 215                 220

Pro Thr Leu Thr Trp Gln Tyr Phe Gly Ser Ala Thr Gly Phe Phe Arg
225                 230                 235                 240

Ile Tyr Pro Gly Ile Lys Trp Thr Pro Asp Glu Asn Gly Val Ile Thr
                245                 250                 255

Phe Asp Cys Arg Asn Arg Gly Trp Tyr Ile Gln Ala Ala Thr Ser Pro
            260                 265                 270

Lys Asp Ile Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu
        275                 280                 285

Arg Met Thr Ile Ala Lys His Thr Ile Thr Thr Ile Leu Asp Thr Leu
    290                 295                 300

Gly Glu Asn Asp Phe Val Asn Ile Ile Ala Tyr Asn Asp Tyr Val His
305                 310                 315                 320

Tyr Ile Glu Pro Cys Phe Lys Gly Ile Leu Val Gln Ala Asp Arg Asp
                325                 330                 335

Asn Arg Glu His Phe Lys Leu Leu Val Glu Glu Leu Met Val Lys Gly
            340                 345                 350

Val Gly Val Val Asp Gln Ala Leu Arg Glu Ala Phe Gln Ile Leu Lys
```

```
        355                 360                 365

Gln Phe Gln Glu Ala Lys Gln Gly Ser Leu Cys Asn Gln Ala Ile Met
    370                 375                 380

Leu Ile Ser Asp Gly Ala Val Glu Asp Tyr Glu Pro Val Phe Glu Lys
385                 390                 395                 400

Tyr Asn Trp Pro Asp Cys Lys Val Arg Val Phe Thr Tyr Leu Ile Gly
                405                 410                 415

Arg Glu Val Ser Phe Ala Asp Arg Met Lys Trp Ile Ala Cys Asn Asn
            420                 425                 430

Lys Gly Tyr Tyr Thr Gln Ile Ser Thr Leu Ala Asp Thr Gln Glu Asn
        435                 440                 445

Val Met Glu Tyr Leu His Val Leu Ser Arg Pro Met Val Ile Asn His
    450                 455                 460

Asp His Asp Ile Ile Trp Thr Glu Ala Tyr Met Asp Ser Lys Leu Leu
465                 470                 475                 480

Ser Ser Gln Ala Gln Ser Leu Thr Leu Leu Thr Thr Val Ala Met Pro
                485                 490                 495

Val Phe Ser Lys Lys Asn Glu Thr Arg Ser His Gly Ile Leu Leu Gly
            500                 505                 510

Val Val Gly Ser Asp Val Ala Leu Arg Glu Leu Met Lys Leu Ala Pro
        515                 520                 525

Arg Tyr Lys Leu Gly Val His Gly Tyr Ala Phe Leu Asn Thr Asn Asn
    530                 535                 540

Gly Tyr Ile Leu Ser His Pro Asp Leu Arg Pro Leu Tyr Arg Glu Gly
545                 550                 555                 560

Lys Lys Leu Lys Pro Lys Pro Asn Tyr Asn Ser Val Asp Leu Ser Glu
                565                 570                 575

Val Glu Trp Glu Asp Gln Ala Glu Ser Leu Arg Thr Ala Met Ile Asn
            580                 585                 590

Arg Glu Thr Gly Thr Leu Ser Met Asp Val Lys Val Pro Met Asp Lys
        595                 600                 605

Gly Lys Arg Val Leu Phe Leu Thr Asn Asp Tyr Phe Phe Thr Asp Ile
    610                 615                 620

Ser Asp Thr Pro Phe Ser Leu Gly Val Val Leu Ser Arg Gly His Gly
625                 630                 635                 640

Glu Tyr Ile Leu Leu Gly Asn Thr Ser Val Glu Glu Gly Leu His Asp
                645                 650                 655

Leu Leu His Pro Asp Leu Ala Leu Ala Gly Asp Trp Ile Tyr Cys Ile
            660                 665                 670
```

```
Thr Asp Ile Asp Pro Asp His Arg Lys Leu Ser Gln Leu Glu Ala Met
        675                 680                 685

Ile Arg Phe Leu Thr Arg Lys Asp Pro Asp Leu Glu Cys Asp Glu Glu
    690                 695                 700

Leu Val Arg Glu Val Leu Phe Asp Ala Val Val Thr Ala Pro Met Glu
705                 710                 715                 720

Ala Tyr Trp Thr Ala Leu Ala Leu Asn Met Ser Glu Glu Ser Glu His
                725                 730                 735

Val Val Asp Met Ala Phe Leu Gly Thr Arg Ala Ser Gly Leu Leu Arg
            740                 745                 750

Ser Ser Leu Phe Val Gly Ser Glu Lys Val Ser Asp Arg Lys Phe Leu
        755                 760                 765

Thr Pro Glu Asp Glu Ala Ser Val Phe Thr Leu Asp Arg Phe Pro Leu
    770                 775                 780

Trp Tyr Arg Gln Ala Ser Glu His Pro Ala Gly Ser Phe Val Phe Asn
785                 790                 795                 800

Leu Arg Trp Ala Glu Gly Pro Glu Ser Ala Gly Glu Pro Met Val Val
                805                 810                 815

Thr Ala Ser Thr Ala Val Ala Val Thr Val Asp Lys Arg Thr Ala Ile
            820                 825                 830

Ala Ala Ala Ala Gly Val Gln Met Lys Leu Glu Phe Leu Gln Arg Lys
        835                 840                 845

Phe Trp Ala Ala Thr Arg Gln Cys Ser Thr Val Asp Gly Pro Cys Thr
    850                 855                 860

Gln Ser Cys Glu Asp Ser Asp Leu Asp Cys Phe Val Ile Asp Asn Asn
865                 870                 875                 880

Gly Phe Ile Leu Ile Ser Lys Arg Ser Arg Glu Thr Gly Arg Phe Leu
                885                 890                 895

Gly Glu Val Asp Gly Ala Val Leu Thr Gln Leu Leu Ser Met Gly Val
            900                 905                 910

Phe Ser Gln Val Thr Met Tyr Asp Tyr Gln Ala Met Cys Lys Pro Ser
        915                 920                 925

Ser His His His Ser Ala Ala Gln Pro Leu Val Ser Pro Ile Ser Ala
    930                 935                 940

Phe Leu Thr Ala Thr Arg Trp Leu Leu Gln Glu Leu Val Leu Phe Leu
945                 950                 955                 960

Leu Glu Trp Ser Val Trp Gly Ser Trp Tyr Asp Arg Gly Ala Glu Ala
                965                 970                 975

Lys Ser Val Phe His His Ser His Lys His Lys Lys Gln Asp Pro Leu
            980                 985                 990
```

Gln Pro Cys Asp Thr Glu Tyr Pro Val Phe Val Tyr Gln Pro Ala Ile
995 1000 1005

Arg Glu Ala Asn Gly Ile Val Glu Cys Gly Pro Cys Gln Lys Val Phe
1010 1015 1020

Val Val Gln Gln Ile Pro Asn Ser Asn Leu Leu Leu Leu Val Thr Asp
1025 1030 1035 1040

Pro Thr Cys Asp Cys Ser Ile Phe Pro Pro Val Leu Gln Glu Ala Thr
1045 1050 1055

Glu Val Lys Tyr Asn Ala Ser Val Lys Cys Asp Arg Met Arg Ser Gln
1060 1065 1070

Lys Leu Arg Arg Arg Pro Asp Ser Cys His Ala Phe His Pro Glu Glu
1075 1080 1085

Asn Ala Gln Asp Cys Gly Gly Ala Ser
1090 1095